

EATING, SLEEPING AND BODY MAINTENANCE

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## SUMMARY OF THESIS

## CHAPTER 1

A theory is put forward in which change in the level of cellular energy charge in response to the differing energy demands of the sleeping/waking rhythm is the fundamental reason why sleep is associated with restorative processes.

Numerous reports from the literature are presented in which the time of sleep is associated with a higher rate of synthesis.

## CHAPTER 2

The literature is surveyed relating eating, sleeping and body maintenance.

Hunger is associated with motor restlessness and feeding with sedation.

Human studies indicate that a bedtime snack of milk and cereal promotes sleep.

Losing weight leads to a reduction whereas gaining weight leads to an increased amount of sleep.



## CHAPTERS 3 and 4

A milk and cereal food (Horlicks) had no effect on sleep, whereas nitrazepam 5mg improved sleep. Withdrawal from the drug led to disrupted sleep.

A placebo pill had no effect on sleep.

Nitrazepam had no significant effect on the plasma growth hormone, glucose, triglycerides or cholesterol, but prolonged Horlicks administration elevated triglyceride levels.

## CHAPTERS 5 to 7

The effects on sleep were compared among a placebo capsule, milk, Horlicks and a drink nutritionally equivalent to Horlicks but containing no milk or cereal. None of the three food drinks had any significant effect on sleep when compared with the inert capsule, but after Horlicks at bedtime sleep was less broken than after the other two food drinks.

The dietary habits of subjects were found to have a considerable influence on how they slept after food at bedtime.

CHAPTERS 8 and 9

Correlational analysis revealed that body weight, but not I.Q. was highly correlated with the mean amount of REM sleep.

CHAPTER 10

It was also found that the mean sleep cycle length correlated with the degree of over or under-weight.

CHAPTER 11

I attempt to answer questions raised by the findings described in earlier chapters.

I tentatively propose a theory linking the maintenance of body weight, sleep cycle length and amounts of REM sleep.

## ACKNOWLEDGEMENTS

It is impossible to carry out sleep experiments, which involve the recording of hundreds of nights, without the help of colleagues and I am greatly indebted to the many people that I have had the pleasure to work with over the last few years.

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I would also like to thank Angela Waters and Morag McRoberts who have helped me greatly in my search through the literature.

Finally I must express my gratitude to Ian Oswald, under whom I have learned so much.



## FOREWORD

In Chapter 1 I attempt to show how sleep plays a vital role in body maintenance. A theory is presented to explain why sleep must be a time of relatively greater synthetic activity and included in the chapter are the numerous examples I myself have found scattered through the literature which show protein synthesis and mitotic proliferation to proceed at their highest rates at the time of rest and sleep.

The studies described in the early chapters appear rather pedestrian, but led to discoveries that I believe to be more interesting.

Although not involved at the inception of the work described in Chapters 3 and 4 I helped to conduct it. I did the calculations and the statistical analyses.

The investigation reported in Chapter 5 marks the beginning of what is strictly my own research. The results were unexpected and because of this I did the post-hoc investigations described in Chapters 6 and 7.

My experiment provided a wealth of normative data and using this I was able to unearth some interesting relationships between sleep and metabolism, which are reported in Chapters 8, 9 and 10.



THESIS MATERIAL WHICH HAS BEEN PUBLISHED

CHAPTER 1

Sleep is for tissue restoration.

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Journal of the Royal College of Physicians 1977, 11:  
376-388.

CHAPTERS 3 and 4

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Nitrazepam: lastingly effective but trouble on withdrawal.

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OSWALD, I.

British Medical Journal 1976, 1: 1558-1560.

CHAPTERS 5, 6 and 7

Dietary habit and sleep after bedtime food drinks.

ADAM, K.

British Journal of Nutrition - submitted 1977

CHAPTERS 8 and 9

Body weight correlates with REM sleep.

ADAM, K.

British Medical Journal 1977, 1: 813-814.

CHAPTER 10

A brain rhythm that correlates with obesity

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British Medical Journal 1977, 2, in press.

EATING, SLEEPING AND BODY MAINTENANCE

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# CHAPTER 1

## HOW SLEEP PLAYS A VITAL ROLE IN BODY MAINTENANCE AND A THEORY TO EXPLAIN WHY THIS MUST BE SO

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## CHAPTER 1

### SUMMARY

I propose that the rest/activity cycle of simple organisms and the sleeping/waking rhythm of higher animals induce concomitant fluctuations in cellular energy charge. In turn the metabolic balance alters such that degradative processes are stimulated during wakefulness and activity and restorative, synthetic processes are inevitably favoured during inactivity and sleep. This hypothesis is presented in broad terms, to apply at all levels of biological integration.

Feeding also induces oscillations in metabolism. In simple organisms, food gathering and motor activity go hand in hand, and the assimilative, synthetic phase is associated with the resting period. Higher organisms do not always rest or sleep after feeding and have evolved complex systems for storage and retrieval of nutrients which allow them to remain active for relatively long periods of time. Nevertheless, I believe the same general principles apply.

## INTRODUCTION

The hungry animal is restless, it goes out to seek for food, and only when satisfied does it lie down to sleep. It assimilates the food and seems restored by its sleep.

In this thesis I shall examine the relationships between feeding, sleeping and restorative processes.

A few years ago Oswald (1969) saw evidence for sleep as a period for restoration and repair of the body and the brain. Restoration or repair must, like growth, depend on protein synthesis. I shall present evidence to support this proposition from over 50 reports showing that rates of protein synthesis or of mitotic division are higher at the time of rest and sleep and shall put forward fundamental reasons why this should be so.

There persists an assumption that degradation and synthesis in tissues not only continue all the time (as they do) but that they are continually equal (which they are not), and upon this invalid assumption has rested much clinical research into protein metabolism. In reality, myocardial proteins of rodents, for example, are synthesized more during the daylight period when they rest and sleep (Rau and Meyer, 1975), and the same is true of epiphyseal cartilage (Simmons, 1968).

Oscillations about a mean are inherent in any system subject to feed-back control, and this is true of living systems. In the simplest organism there are oscillations between food-engulfing activity on the one hand and inactivity with assimilation on the other. There will too be oscillations between a state in which degradative chemical processes are accelerated and one in which synthetic processes are enhanced.

I propose that it is the differing energy demands of the activity/inactivity rhythm that chiefly determine the degradative/synthetic rhythm, such that the synthetic period inevitably coincides with the inactive or rest period, and that this is equally true in higher organisms in which a central nervous system ensures rest's integrity through positive unresponsiveness during sleep and that such relationships, present throughout the animal kingdom rely upon the fundamental metabolic co-ordinator, the cellular energy charge. The energy charge is a measure of the available free energy in the form of ATP.

Figure/



Figure 1.1 summarizes in simple terms the proposition that, as cellular work is reduced energy charge reaches higher levels and so protein synthesis will be favoured and degradative processes will diminish. Cellular work includes the processes involved in motor activity, the maintenance of ion gradients and active transport systems - all of which use up ATP and so tend to lower the energy charge. The demands of cellular work are thus in competition with the needs of synthesis for ATP.

Feeding must play a vital role in this interplay, for food supplies the substrates for energy production and the building materials for the synthesis of structural and storage macromolecules. The intracellular fate of the digestion products of food will depend on the metabolic balance within cells and in higher forms of life the assimilation of ingested food will also depend on the hormonal environment, for the endocrine systems of the body exert powerful effects on metabolic processes in general and influence the requirements for the various nutrients. At least, in man the normal hormonal pattern complements the more fundamental rhythms associated with the sleeping/waking cycle.



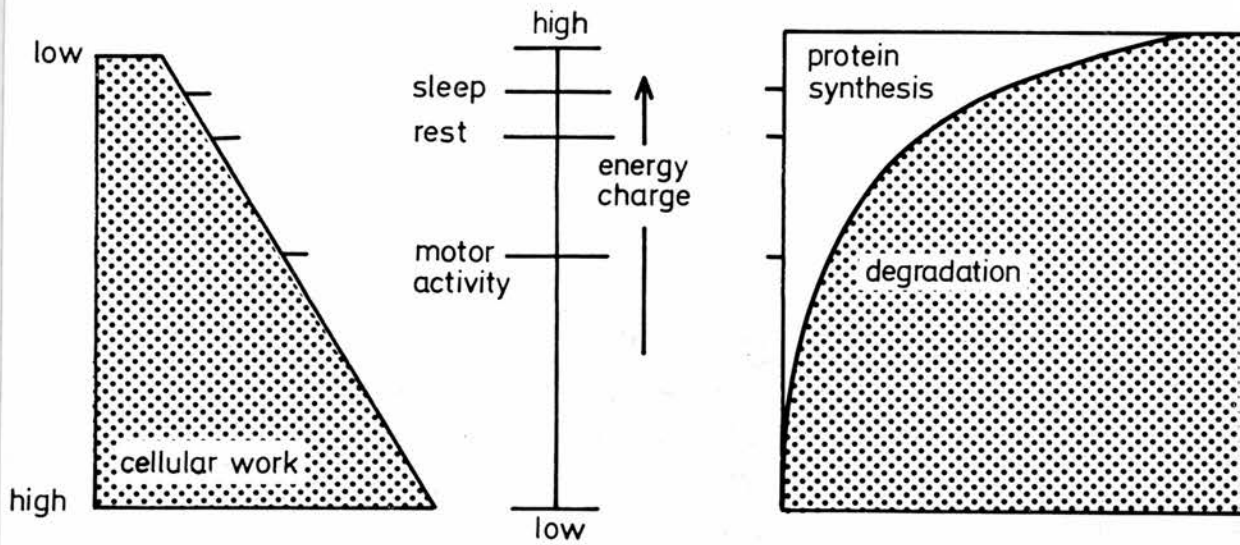


FIGURE 1.1 When the rate of cellular work is low during sleep, energy charge rises. This higher level of energy charge stimulates protein synthesis and reduces the rate of degradative processes, whereas when cellular work proceeds at a high rate such as during motor activity, energy charge falls. Lower levels of energy charge inhibits the rate of protein synthesis and accelerates degradative processes.

(I) ACTIVITY/INACTIVITY RHYTHMS AND  
THE ENERGY CHARGE

(a) Rates of synthesis and degradation controlled by energy charge.

To sustain life an organism has to maintain a chemical composition that differs from its surroundings and to do so it must expend energy. It must repair its structural molecules and it must reproduce, both of which involve biosynthetic, energy-using processes, reproduction requiring cell-division as well. The necessary energy is furnished by the catabolism of food and fuel stores to yield ATP (adenosine triphosphate) and is released by cleavage of the terminal phosphate(s), leaving ADP or AMP (the adenosine di- and mono-phosphates). These energy-releasing reactions are enzymically coupled to synthetic reactions, to supply the energy that drives them. The adenine nucleotides, AMP, ADP, and ATP, accept, store and transfer chemical potential energy and constitute a link among all the cell's activities. These include the maintenance of chemical gradients (e.g.  $\text{Na}^+/\text{K}^+$  pumps), active transport, and energy for motor activity. Hence the adenine pool is a link between activity/inactivity rhythms and the catabolic/anabolic balance of the cell.

To/

To achieve co-ordination, some universal, internal signal must operate to enhance or inhibit the cell's chemical activities, all of which can be broadly divided into energy-yielding (ATP-producing) reactions and energy-using (ATP-depleting) processes. It is the energy state of the cell that provides that signal. Its influence on metabolic pathways has been defined by Atkinson (1968), who proposes that the energy charge,  $EC = \frac{ATP + ADP/2}{ATP + ADP + AMP}$  of a cell varies within a range up to unity. Lower values of EC favour ATP-producing pathways and higher values of EC promote ATP-utilising sequences.

The loci of control are regulatory enzymes that are sensitive to the levels of the adenine nucleotides and catalyze the irreversible steps in biochemical sequences. Every pathway has at least one such step, without which no net flux could occur. Irreversible steps mean that the end-product of a synthetic sequence is not degraded by the reverse of the synthetic pathway, and hence the rates of synthesis and degradation can be controlled by a single signal which modifies the activities of the regulatory enzymes in both synthetic and degradative pathways simultaneously. The EC level provides such a signal and affects these pathways in opposite ways. Degradative pathways yield ATP and so raise/



raise the EC of a cell. A higher level of EC then acts as a signal to reduce the rate of degradation.

Synthetic pathways depend on ATP to drive them and are promoted by higher levels of EC. If EC falls then it is a signal to increase degradation and curtail synthesis, as the system tries to restore a higher EC, which is thermodynamically more stable (Goldbeter, 1974).

Figure 1.2 shows the typical response to changes in EC of the rates of reaction of regulatory enzymes in synthetic and degradative pathways. The control enzymes have response curves with steeper slopes in the region of higher EC and physiological values lie in the highly responsive, "cross-over" portion of the graphs (Chapman et al., 1971; Atkinson, 1970) where small changes in EC can disproportionately alter the relative rates of synthesis and degradation. In addition, both types of EC response curves can be modified by the concentration of the biosynthetic end-product in such a way that if, for example, a synthetic end-product were in short supply, then the responsiveness to EC of the control enzymes in the synthetic pathway would be increased and synthesis enhanced (Figure 1.3).

A/



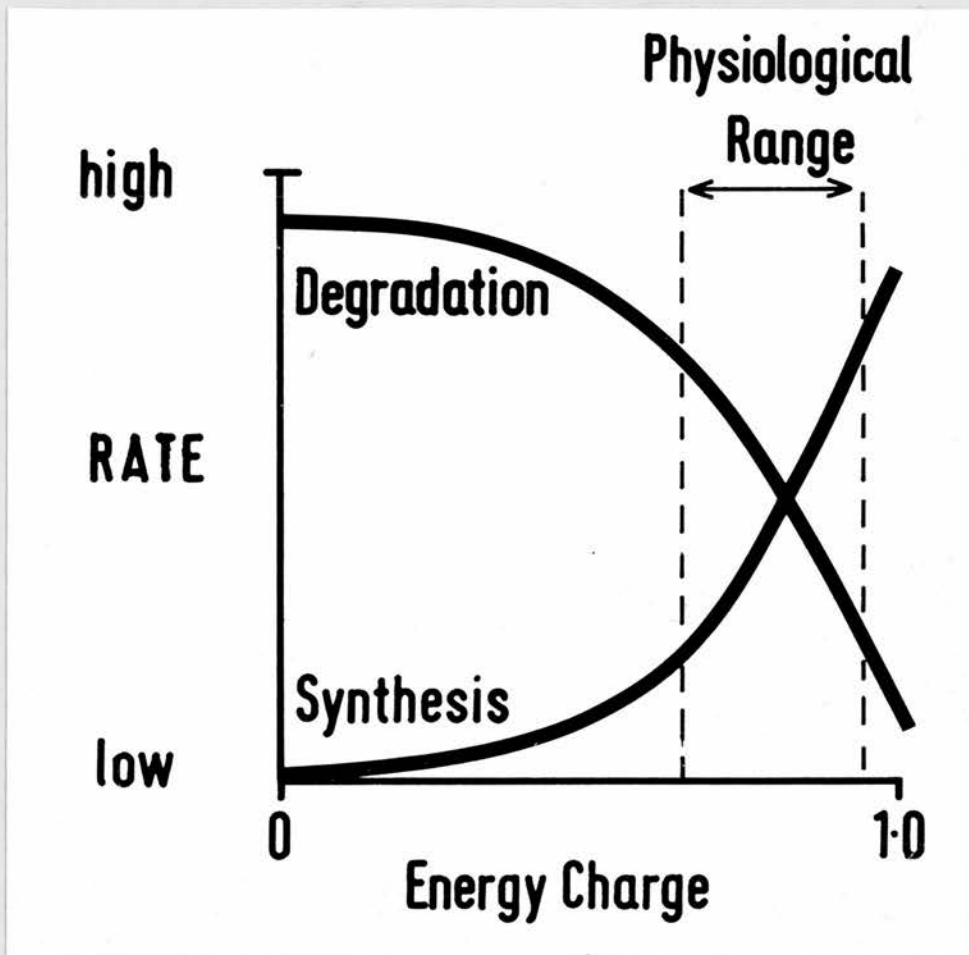


FIGURE 1.2 Typical curves of the rates of reaction of control enzymes in synthetic and degradative pathways in response to different levels of cellular energy charge.

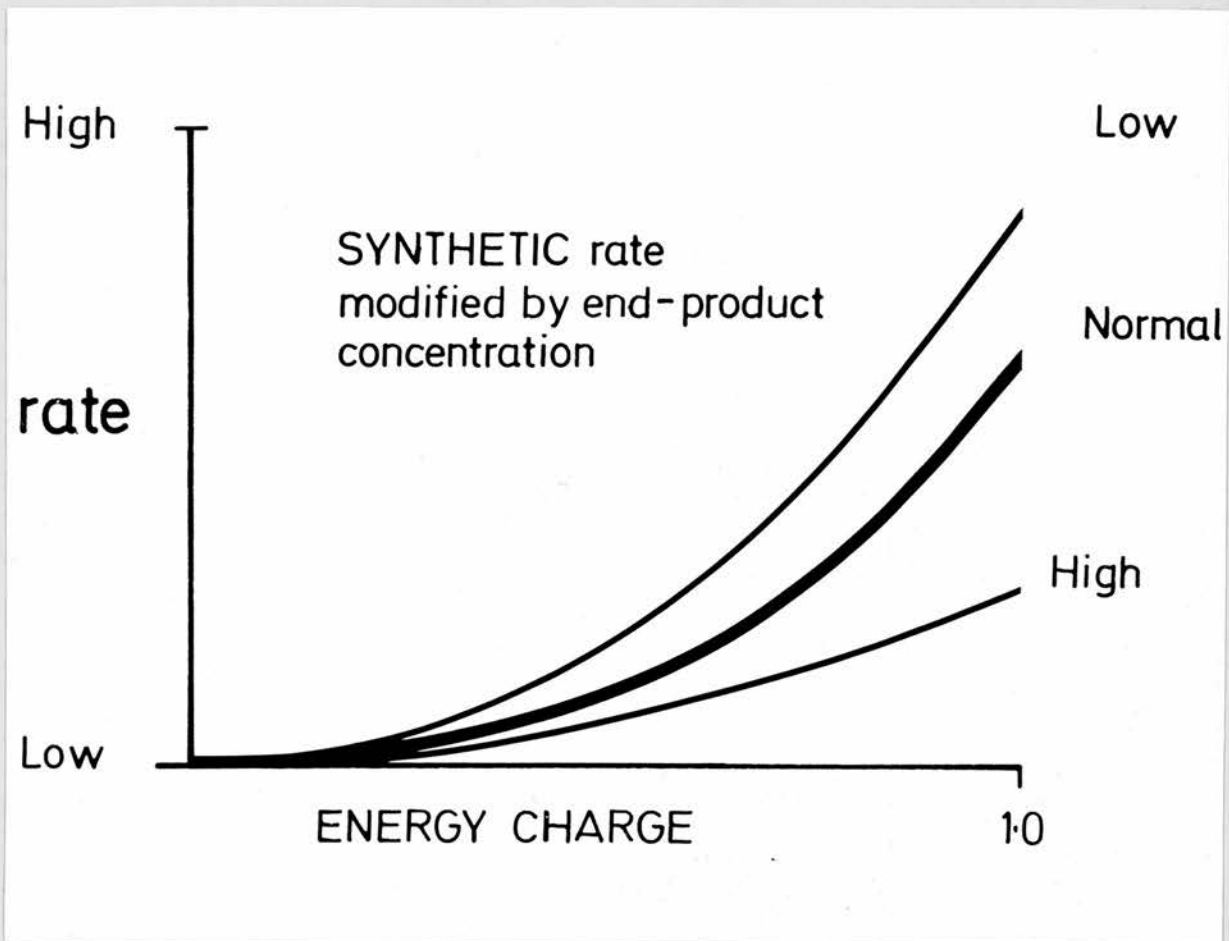


FIGURE 1.3 Typical rate of reaction of a synthetic pathway in response to different levels of cellular energy charge and the modification of this response by high and low concentrations of synthetic end-product.

A prediction from this theory is that energy metabolism (degradation) and synthetic processes will, in broad terms, exhibit predictable rhythmic variations which are oppositely phased so that when one rhythm has a peak the other shows a trough. Later in this chapter I present many examples of peaks in synthetic activity at the time of rest and sleep. There is some evidence that degradative processes do show the opposite pattern. A 24h rhythm of oxygen consumption has been found in starving birds, which when kept in darkness exhibited very little motor activity, and yet the lowest rates of oxygen consumption occurred at the time of day when these birds sleep (Aschoff and Pohl, 1970). The rate of weight loss in a starving swift was found to be least at night (at the time of sleep) and to parallel the body temperature rhythm (Koskimies, 1950). Both these studies point to a 24h rhythm of degradative metabolism.

(b) Protein synthesis, growth and activity.

The concept of energy charge was originally applied to intermediary metabolism but other processes too are sensitive to EC. The sensitivity of steps in protein synthesis to changes in adenine nucleotides (Walton and Gill, 1975; Ayuso-Parrilla and Parrilla, 1975) are of particular/



particular interest, as are the changes in EC that are synchronized with growing and non-growing phases of *E. Coli* (Chapman et al., 1971). Such synchronized changes illustrate how EC correlates with anabolic processes.

It is proposed that the simple organism's oscillations between rest and activity must induce concomitant oscillations in EC and so, in turn, in other cellular processes. Motor activity demands ATP and hence motility and food-gathering will lower EC, promote degradative processes, temporarily suppress biosynthesis and result in a relatively low concentration of protein. After taking in sufficient nourishment it would be economical to rest, the EC would rise and conditions would be optimal for the biosynthetic processes previously curtailed, and these would be the greater because of the added signal of low protein concentration.

Evidence that motility does inhibit synthetic processes can be seen in an experiment where the unicellular *Stentor coeruleus* was cut in half, such that each half received an equal share of the macronucleus, but only one half had the ciliary apparatus. Subsequent onset of mitotic activity occurred much earlier in the cilia-free end (Guttes and Guttes, 1959). The EC must have risen during the enforced rest of the non-ciliated end and acted as a trigger for synthetic processes.

(c) Synthesis during rest in higher organisms.

In complex organisms, motility and responsiveness to the environment are not characteristics of each cell, but the same principles apply. Responsiveness, through the information-carrying system, is energy-consuming, and so tends to lower the EC. The house cricket, *Acheta domesticus*, has a 24h rhythm of RNA and protein synthesis in its brain and sub-oesophageal ganglion, with synthesis highest when these insects are inactive. Their activity increases sharply with the onset of darkness, whereupon synthesis of RNA and protein in the brain falls to its lowest (Cymborowski and Dutkowski, 1969, 1970).

Higher organisms store fuel foods to allow prolonged activity without feeding. As in simple organisms, the optimal time for synthetic processes would be during a rest/sleep period following feeding. Many higher animals are observed to rest/sleep after feeding and indeed feeding and sleeping have been shown in many investigations to be inter-related (See later in this thesis).

During activity the energy-requiring, biosynthetic pathways would be suppressed by a downward shift in the EC, which would simultaneously stimulate catabolic processes in tissues directly involved (e.g. muscles) and/

and those linked metabolically (e.g. liver and adipose tissue). Even more tissues would be influenced if their substrates for ATP production and synthesis of macromolecules were diverted as fuel for motor activity. Contracting muscle in vitro has a lower ATP concentration than resting muscle, despite a tripling of oxidative metabolism (Crabtree and Newsholme, 1972; Newsholme and Start, 1973). Likewise, brief exercise considerably reduces the EC of rat skeletal muscle in vivo (Wojciechowska et al., 1975). The concentration of ATP in biopsies taken from human muscle after 2 min of exercise is 25% less than from resting controls (Karlson and Saltin, 1970). Conversely, the in vivo rate of protein synthesis in rat diaphragm muscle is highest during the resting/sleeping period (Rebolledo and Gagliardino, 1971). It has been shown in man that exercise enhances the output of alanine from muscle and its subsequent re-uptake by the liver where it is a gluconeogenic precursor (Ahlborg et al., 1974). As examples of tissues linked indirectly the rate of protein synthesis falls in the hypothalamus if rats exercise (Bordeianu and Butculescu, 1971) and protein synthesis in rat skin is at its highest during the daylight, when rats rest and sleep (Chekulaeva, 1969).

The/



The effect of 30 min of exercise, on the incorporation rate of radioactive methionine into liver, kidney, heart and muscle protein, was studied in groups of young and old rats (Mateev et al., 1967). Control rats for each age group were compared with experimental rats sacrificed during exertion and with others sacrificed at 30 min intervals up to 5h following the period of exercise. During motor activity biosynthesis sharply decreased. In young rats the suppression of amino acid incorporation into protein in heart, liver and muscle lasted for several hours after the exertion ceased and for over an hour in kidney, whereas the suppression following exercise in older rats did not return to control values within the 5h period in any of the tissues investigated.

In man exercise inhibits skin mitosis for many hours afterwards (Fisher, 1968) and under certain circumstances has been shown to induce protein catabolism by Molé and Johnson (1971), who found a paradoxical effect of surfeit feeding on protein metabolism; it was anabolic at rest but catabolic following exercise.

Peaks in mitotic rate in frog crystalline lens epithelium coincide with episodes of motor inactivity whereas/

whereas troughs are associated with active periods (Kuznetsov et al., 1972). It is important to distinguish such phenomena from the increased use of tissues that leads to their subsequent hypertrophy. The latter involves the activation of genetic material in the nucleus, with increased formation of RNA, and subsequently of proteins many hours later (Meerson, 1975).

(d) Mitosis and ATP.

Mitosis depends upon synthesis, whether for tissue maintenance or propagation of the species. There is a strong relationship between mitotic activity and higher concentrations of ATP (Guttes and Guttes, 1959). A fall in ATP below a critical level inhibits mitosis (Epel, 1963). A positive correlation between the rhythm of ATP level and cell division has been shown for *Tetrahymena pyriformis* (Plesner, 1964). Moreover, most tissues have a 24h variation of mitotic rate, with the maximum during the resting/sleeping period, when, as we must suppose, ATP and EC levels are highest. Examples are listed in Table 1.1.

It could be that through evolution the rhythms of energy-dependent mitotic proliferation were entrained to/

TABLE 1.1 MITOSES MAXIMAL DURING THE TIME OF REST AND SLEEP

Species	Tissue	Reference
<b>Ectodermal Tissues</b>		
Man	Epidermis	Cooper and Schiff (1938); Scheving (1959); Fisher (1968)
Mouse	Epidermis	Halberg et al. (1965)
Rat	Epidermis	Chekulaeva (1969)
Rat	Healing epidermis	Gololobova (1960)
Rat	Corneal epithelium	Sigelman et al. (1954)
Mouse	Corneal epithelium	Vasama and Vasama (1958)
Frog	Crystalline lens epithelium	Kuznetsov et al. (1972)
Rat	Pineal parenchyma	Renzoni and Quay (1964)
Rat	Anterior pituitary	Nöuet and Kujas (1975)
Hamster	Cheek pouch epithelium	Brown and Berry (1968); Izquierdo and Gibbs (1972)
Rat	Sebaceous gland cells	Bertalanffy (1957)
Rat	Lacrimal, parotid and submandibular glands	Vonnahme (1974)
Pregnant mice	Mammary alveolar epithelium	Echave Llanos and Piezzi (1963)
Rat	Lip epithelium	Bertalanffy (1960)
Rat	Buccal mucosa	" "
Rat	Anal epithelium	" "
<b>Mesodermal Tissues</b>		
Man	Bone marrow	Mauer (1965)
Rat	Epiphyseal cartilage	Simmons (1964)
Rat	Bone marrow	Clark and Korst (1960); Hunt and Perris (1974); Uryadnitskaya (1974)
Mouse	Bone marrow	Clark and Korst (1969)
Rat	Kidney tubules	Sharipov (1967); Saetren (1972)
Rat	Thymus	Hunt and Perris (1974); Kirk (1972)
Rat	Inner enamel epithelium, incisor teeth	Gasser et al. (1972a)
<b>Endodermal Tissues</b>		
Rat	Liver parenchyma	Vonnahme (1974); Jaffe (1954)
Mouse	Liver	Barnum et al. (1958)
Rat	Tongue	Gasser et al. (1972b)
Mouse	Squamous epithelium of tongue and oesophagus	Burns et al. (1976)
Rat	Rectal mucosa after injury	Reeve (1975)
Rat	Gastric epithelium	Clark and Baker (1962)
Rat	Lung interalveolar septa	Romanova (1966)
Rat	Duodenum	Scheving et al. (1972)
Mouse	Duodenum	Scheving et al. (1972)
Mouse	Colon	Chang (1971)



to the variations in energy state associated with the rest/activity cycle. The hormones of higher organisms are sophisticated additions to more primitive controls but where investigated they are found to be complementary (Bullough, 1948; Sigelman et al., 1954; Fisher, 1968; Vonnahme, 1974).

( II) FEEDING AND SYNTHESIS

Feeding also induces oscillations in metabolism and in higher organisms it is the liver that has to deal with the influxes of nutrients so that there are not wide variations in the blood levels of the various nutrients.

When a protein meal is fed to dogs more than half of the incoming amino acids are degraded to urea, a small proportion are retained as liver protein, some are secreted as plasma proteins and only about a quarter of the incoming load passes into the general circulation as free amino acids (Elwyn, 1970).

The 24h rhythm of net protein synthesis in rat liver (Richardson and Rose, 1971) is the only instance that I found in the literature of a peak in synthetic rate occurring during the activity period. It can be readily understood why this organ should be the only exception for, in response to an increased amino acid supply, protein synthesis in the liver is accelerated, while protein breakdown is reduced (Munro et al., 1975) which results in the accumulation of enzymes with short half-lives involved in the metabolism of the incoming nutrients. In consequence there are diurnal rhythms in the synthesis of liver proteins, and in the accumulation and breakdown of liver RNA, which are both related to the intermittent intake of meals containing protein (Munro et al., 1975).

The/

The plasma levels of amino acids are also affected by dietary carbohydrate through an insulin-dependent mechanism. Within about an hour of consuming carbohydrate the level of most plasma amino acids decrease, owing to deposition in muscle through insulin-mediated transport (Munro et al., 1959). Muscle represents the major depot for retention of free amino acids in the body (Munro, 1970) but deposition of amino acids in muscle does not necessarily lead to an increase in protein synthesis rate for protein synthesis depends on many things and especially on the intracellular ATP levels.



### (III) SLEEP PROMOTES SYNTHETIC PROCESSES

#### (a) Sleep is more than rest.

Rest reduces ATP depletion but sleep is more than rest, it is a state of unresponsiveness brought about by active nervous mechanisms, a highly-developed form of rest that ensures that the whole body, including the nervous system, has an opportunity to recuperate.

There are two types of sleep that alternate, one being named NREM, or orthodox sleep, and the other REM or paradoxical sleep. Human NREM sleep is divided into stages 1-4, according to the electroencephalogram. Stages 3 and 4 are called slow-wave sleep, or SWS. The stages differ in their degrees of unresponsiveness, with stage 2 being a less responsive state than stage 1, SWS a state of even lesser responsiveness, while REM sleep is about equal to stage 2 (Figure 1.4). These relationships in the degree of responsiveness are true for responses to auditory stimuli (Williams et al., 1966), blood pressure reflexes (Coccagna et al., 1971), or scratching by patients with itchy skins (Savin et al., 1975). In harmony with the differing degrees of responsiveness, the same relationships are true also of the metabolic rates that accompany these sleep stages. Human metabolic rate is some 10% lower in stage 2 than in/

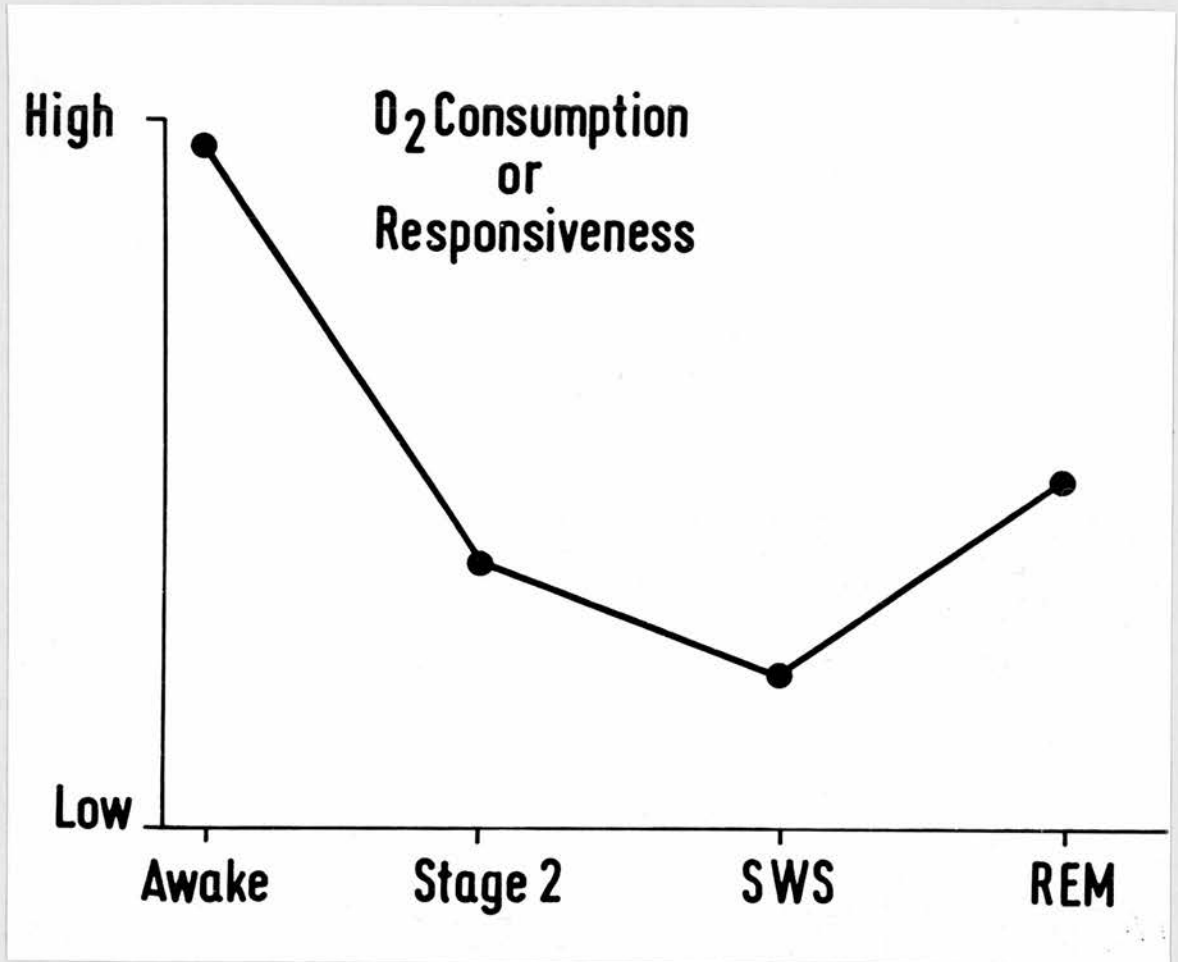


FIGURE 1.4 In stages 3+4 (slow wave) sleep, responsiveness is lowest to auditory signals, scratching is least, blood pressure is lowest, and whole-body oxidative metabolism is lowest: the demands of cellular work, that compete with the needs of synthesis, are at their lowest.

in wakeful rest, with a further 2% fall during SWS (Breibbia and Altshuler, 1968). Evidence that merely resting in bed is no substitute for sleep is indicated by the results of Lubin et al. (1976). They compared three groups of young men on a schedule 60 min of treatment alternating with 160 min of testing. The regime was kept up for 40h. Three different treatments were compared; one group were allowed to sleep during the 60 min treatment periods, and another group exercised on bicycles. A third group lay resting on a bed, but were not allowed to sleep, during the 60 min periods. During the 160 min testing sessions all groups listened to a 40 min auditory vigilance task, did an arithmetic test, had their short-term memory tested for digits and words, rated their mood and rated how sleepy they felt. The bed rest group showed significant impairment on all eight measures and the authors concluded that bed rest is no substitute for sleep. The exercise group's performance was worse on all measures than either of the other groups and suggests that exercise exacerbates the detrimental effects of sleep loss. Impairment of physical performance by sleep deprivation was illustrated in another study where motor performance in teenagers was tested across 50h of sleep deprivation/



deprivation (Copes and Rosentswieg, 1972). The results showed a downward trend in performance as the deprivation progressed, on such tests as the Harvard step test, time to run a variety of races, length jumped, reaction time and strength measured by the time the ~~youngster~~ was able to hang from a beam with bent arms, supporting his/her entire weight. One night of sleep following the deprivation period restored their performance on all these tests to normal.

(b) Sleep for growth and repair.

In an analysis of data from 53 species Zepelin and Rechtschaffen (1974) found a positive correlation between daily sleep durations and metabolic rates. Their interpretation was in terms of energy conservation, but, it can be seen from another viewpoint, the higher the rate of metabolism (and hence degradation) during the active period, the longer would be the sleeping period needed for compensatory synthesis. In individual men the customary duration of sleep correlates positively with waking body temperatures, and hence presumably with waking metabolic rate (Taub and Berger, 1976). Growth too depends upon synthetic functions and in one investigation it was found that a group of children of short stature had grown only one-third as fast at times of poor/

poor sleep as of good (Wolff and Money, 1973).

Growth and repair necessarily depend on net protein synthesis and so a positive nitrogen balance. Rudman et al., (1973) found that more nitrogen was retained in humans deficient in growth hormone following an injection of growth hormone (GH) at 2300h than after a similar dose at 0800h suggesting that subsequent sleep facilitated nitrogen retention and presumably growth in GH deficient children. On the other hand sleep deprivation for two nights in 19 young men led to a significant increase in nitrogen excretion on the second day of deprivation, which continued at high levels during the first post-deprivation day and on the second post-deprivation day fell to below baseline levels. (Schrimshaw et al., 1966). Throughout the study nitrogen intake was constant. Sleep deprivation must be stressful (Kuhn et al., 1969) and so elevated corticosteroids probably contributed to the increased nitrogen excretion. Nevertheless the results suggest that sleep deprivation enhanced protein and/or amino acid catabolism. The apparent time delay before nitrogen excretion increased following the commencement of sleep deprivation was probably a reflection of the inertia in urea excretion. Growth and repair of course also depend on the ingestion of a diet adequate in both energy/

energy and protein but the fate of ingested food depends on the metabolic conditions prevailing during the assimilative period. The metabolic conditions depend on the short and long term nutritional status, the extent of motor activity, the time of the 24h and the hormonal environment, factors which are, inevitably interdependent.

Even during total starvation more amino acids are excreted in the urine over the hours 0800-1100h than between 0200h and 0500h (Tewksbury and Lohrenz, 1970) and the same pattern is found for the degradation of tryptophan (Rapoport and Beisel, 1968). Normal subjects have been shown to have a 24h rhythm in their plasma amino acid levels, with peaks during the day and with lowest levels around 0200h. The rhythm persisted in subjects fed a protein-deficient diet (Wurtman et al., 1968a). The latter condition distinguishes the tyrosine amino acid rhythm from the rhythm of activity of the hepatic enzyme, tyrosine transaminase, which is extinguished by a protein deficient diet (Wurtman et al., 1968b). The biological significance of the rhythm of amino acid levels is unclear but it may represent a stimulation of the uptake of amino acids into tissues at certain times of the 24h. It is thus interesting that altering the sleeping/



sleeping period from 2200h - 0600h to 1000h - 1800h caused a rapid (within 48h) shift in the hour of peak plasma concentration of amino acids - to 0400h i.e. into the new activity period (Feigin et al., 1968). The hormonal environment too depends on the time of the 24h and on the sleep wake rhythm.

(c) The hormones of sleep.

The large nocturnal secretion of human growth hormone (GH) (Takahashi et al., 1968; Honda et al., 1969), is dependent upon the presence of sleep and especially SWS (Sassin et al., 1969a; Schnure et al., 1971). This itself reveals sleep as a time that facilitates anabolic processes in man, since GH stimulates amino acid uptake into tissues, promotes protein and RNA synthesis (Korner, 1965) and has wide inter-reactions, such as stimulating red blood cell formation indirectly through erythropoietin (Peschle et al., 1972). It raises blood free fatty acids, whose subsequent degradation is a source of cellular energy (ATP), thereby saving amino acids from catabolism and increasing their availability for protein synthesis during sleep.

Corticosteroids/

Corticosteroids reduce net protein synthesis (Ardeleanu and Sterescu, 1973; Friedman and Strang, 1966) and nocturnal GH comes at that time in the 24h when corticosteroids are lowest (Weitzman et al., 1971). Consequently, even greater protein synthesis occurs during human sleep, as demonstrated by Rudman, et al. (1973) who injected GH and found significantly greater nitrogen retention after a 2300h dose than after a dose at 0800h.

Three other sleep-dependent hormones are known: prolactin (Sassin et al., 1973), luteinizing hormone and testosterone (Boyar et al., 1972, 1974; Rubin et al., 1973a, 1976): all four hormones released by sleep are thus hormones that promote anabolism. Other hormones can alter the metabolic balance within target cells, and so, maybe, they too can influence the EC level and then, indirectly, protein synthesis.

(d) Slow-wave sleep for compensatory restoration.

It has been suggested that sleep may have compensatory features for the degree of waking activity. After sleep-deprivation, men have extra SWS (Berger and Oswald, 1962; Williams et al., 1964), and monkeys extra GH (Jacoby et al., 1975a). The longer the wakefulness/

wakefulness prior to a nap, the more SWS and GH (Karacan et al., 1974). Even one hour of extra wakefulness during the night is followed by extra SWS and GH in the later night (Beck et al., 1975). Extra exercise leads cats to have more SWS (Hobson, 1968), ordinary men to get more GH (Adamson et al., 1974), and athletes greater amounts of SWS (Baekeland and Lasky, 1966; Shapiro et al., 1975; Maloletnev and Telia, 1975; Zloty et al., 1973; Maloletnev et al., 1977).

Thyroid hormone increases degradation and whereas hypothyroid patients lack SWS (Kales et al., 1967a), hyperthyroid patients have an excess of it and more GH (Dunleavy et al., 1974). After days when normal men have had higher thyroxine secretion they get more SWS (Johns et al., 1975). Acute starvation increases both SWS (MacFadyen et al., 1973) and GH (Parker et al., 1972; Karacan et al., 1973) at a time when the latter's protein-sparing action would be of importance, while after chronic starvation an increase of SWS is associated with tissue-rebuilding (Lacey et al., 1975). As earlier mentioned, SWS will also be most strongly associated with anabolic repair because metabolic rate is then at its lowest and EC therefore likely to be highest.

The/



The EEG waves have, of course, multiple determinants and so SWS may be seen as a time that is simply facilitatory for enhanced synthesis. Durations of electrical slow waves may be in part genetically dictated or altered by disease, without immediate regard to restorative needs.

#### (IV) SLEEP AND THE BRAIN

##### (a) Sleep - a state of unresponsiveness

It is the brain that controls sleep and it is brain functions such as the power to sustain attention that are most obviously impaired by sleep deprivation. Although the mature brain no longer grows it still needs synthetic activity. It rivals the liver in its high rate of turnover of proteins and nucleic acids consistent with its role in information-processing, storage and retrieval, which rely on synthetic activity over and above the protein synthesis required for enzymes and renewal of structural components. The benefit of sleep is most obvious for the brain, since during rest the nervous system remains responsive to the environment, whereas in sleep it becomes unresponsive (Steriade, 1970). The responsiveness of the wakeful cortex depends upon sustained ascending activation from the mesencephalic reticular formation, and the high levels of extracellular  $K^+$  so caused (Katzman and Grossman, 1975). These higher levels of  $K^+$  are closely coupled to higher energy consumption by the ATPase ion pump (Bachelard, 1975a; Jobsis et al., 1975; Lowry, 1975). Higher extracellular  $K^+$  implies that intracellular  $K^+$  levels have been lowered.

Cerebral/

Cerebral protein synthesis is sensitive to intracellular  $K^+$  concentration. A rise in intracellular  $K^+$  concentration from 25mM to 80mM resulted in a six fold increase in the rate of protein synthesis (Roberts and Zomzely, 1966).

Sleep-deprivation impairs mental functions and as the deprivation continues there is an increasing 'pressure' to sleep, which suggests some deficit in cerebral re-charging or repair. Figure 1.3 enables one to understand why, after prolonged sleep-deprivation, restoration can be accomplished in fewer hours than those lost.

#### (b) Synthesis and energy charge

Brain protein synthesis has its highest rates at the time when rats rest and sleep (Richardson and Rose, 1971; Rose et al., 1969; Gordon and Scheving, 1968). The cat has several sleep periods and with each of these there is a rise in the protein content of perfusates from the brain (Drucker-Colin et al., 1975a). Jones (1971) found brain ATP levels of golden hamsters were higher during sleep.

The parallelism that exists between the rate of RNA synthesis and the ATP concentration in brain slices/



slices and the fact that the ATP concentration for optimal amino acid incorporation by microsomal and ribosomal preparations is more critical in the cerebral cortex than in similar preparations from liver (Zomzely et al., 1964) both suggest that the cell content of available ATP is the regulating factor in brain protein synthesis (Itoh and Quastel, 1969).

The protein and RNA content of supra-optic nuclei was higher in sleeping rats than waking rats, while the latter in turn had a higher content than sleep-deprived animals (Doemin and Rubinskaya, 1974). Van den Noort and Brine (1970) measured the ATP, ADP and AMP concentrations in rat brain after 13h of sleep-deprivation and after 1h of subsequent sleep. Calculations of EC using their results give a value of 0.77 after 13h of sleep deprivation but 0.83 after the 1h of sleep. This rise is in the highly responsive portion of the curve and Figure 1.3 illustrates how protein synthesis in the brain would differ under these two conditions and how there could be additional enhancement of protein synthesis during sleep at a time when end-product concentration would presumably be low.

(c) NREM-REM sleep cycles and protein synthesis.

The different physiology of NREM and REM sleep suggests that they differ in function but a causal relationship has been proposed because NREM always precedes REM sleep (Hartmann, 1973). The leading ATP user of the brain is the  $\text{Na}^+/\text{K}^+$  ATPase pump (Bachelard, 1975a), the rate of activity of which is determined by the rate of neuronal-firing (Lowry, 1975). During SWS the majority of neurones have a much reduced firing-rate compared with waking (McGinty et al., 1974). As a result of this low rate, ATP depletion would be reduced and EC level would rise, whereas during subsequent REM sleep the higher firing-rate (McGinty et al., 1974) would lower intracellular ATP and stimulate brain glycolysis and respiration. The firing-rate during REM sleep approximates to waking but this is not in response to the outside world and may represent transfer of information among neurones.

The amount of REM sleep seems to be correlated with the intensity of brain synthetic activity (Oswald, 1969, 1970, 1976; Stern and Morgane, 1974). If higher rates of protein synthesis occur during REM sleep itself in conjunction with the higher rate of cell-firing, this would imply compartments of ATP pools between, for example, neurones and glia, or intracellular compartments within neurones, as there is for glucose transport (Bachelard, 1975b).

In/

In higher organisms, protein is synthesized at the rate of two amino acids per sec, which means 1-2 min to synthesize a medium-sized protein molecule (Dintzis, 1961), in addition to the time required to initiate the process. Oscillations have been found in the rate of protein synthesis in a remarkable diversity of tissues (Brodsky, 1975). There is a theoretical minimum oscillation period of the order of minutes, because of the inertia in the protein synthetic machinery (Goodwin, 1963). The REM periods of most species last only a few min, and this is so short a time that the onset of a REM period could hardly be the primary initiator of any increased brain protein synthesis associated with that period. Possibly, peak rates of brain protein synthesis might coincide with the onset of REM periods, conditions for stimulating the peaks having been generated during the preceding SWS, when cell-firing would have been at a minimum and when, therefore, EC would have risen.

It has been assumed by many (e.g. Drucker-Colin et al., 1975a) that REM sleep stimulates protein synthesis, but could it not be the other way round, with peaks in protein level or rate of synthesis stimulating the occurrence of REM sleep? There is some evidence to suggest that this may be the case. Prolonged/



Prolonged fasting in adult rats greatly reduced the conversion of glucose to protein (Barkai et al., 1974) and feeding deoxyglucose (which cannot be metabolised) caused a decrease in amount of REM sleep in rats. (Panksepp et al., 1973). Injection of bovine growth hormone into rats resulted in a temporally related increase in REM sleep and increased levels of whole brain soluble proteins (Drucker-Colin et al., 1975b) whereas a similar molecular weight protein, thyrotropin, had no effect on the amount of REM sleep. Anisomycin reduced the amount of sleep, but it was REM sleep in particular that was significantly reduced. There was also a time-dependent decrease in brain protein levels. Administration of growth hormone at the same time as the antibiotic returned sleep to control levels, suggesting that extra growth hormone can compensate for the detrimental effects of the drug.

In humans the effect on sleep patterns of administering glucocorticoid has been investigated by Gillin et al. (1972). They found a dose-related reduction in the amount of REM sleep. Corticosteroids are known readily to penetrate into the brain tissue (Peterson and Chaikoff, 1963) and as these hormones promote protein catabolism (Ardeleanu and Sterescu, 1973; Friedman and Strang, 1966) it may be that a reduction/

reduction in net protein synthesis led to the decrease in REM sleep. So there does appear to be some evidence to support the proposition that peaks in brain protein concentration may stimulate REM sleep. And it is tempting to speculate with Brodsky (1975) that oscillations in the rate of protein synthesis underlie NREM-REM cycles.

CHAPTER 2

A SURVEY OF THE LITERATURE RELATING EATING  
SLEEPING AND BODY MAINTENANCE

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## CHAPTER 2

### SUMMARY

Evidence from the animal literature suggests that lack of food is associated with increased motor restlessness but that after feeding an animal is more likely to fall asleep.

Human studies indicate that sleep is less restless or less disrupted by waking when a small meal of milk and cereal is taken prior to retiring to bed.

Loss of body weight in man and animals is associated with a decreased amount of sleep, and gain in weight in humans leads to an increased amount of sleep.

(I) EVIDENCE THAT NUTRITIONAL STATUS INFLUENCES SLEEP

(a) Hunger associated with increased restlessness

Many years ago Richter (1922) demonstrated an increase in the daily activity of the rat when deprived of food over a prolonged interval. He found that activity increased up to the third day of deprivation and thereafter declined.

In a similar study Siegel and Steinberg (1949) measured the activity level in groups of rats deprived of food for 12, 24, 36 and 48h. They found that the level of motor activity increased as a negatively accelerating function of the length of time without food. More recently Treichler and Hall (1962) measured motor activity in two groups of rats, using an activity wheel. One group of 15 rats, fed ad lib, served as controls to indicate the weight gain expected in rats of this age. The other group of 30 rats were subdivided into three groups of ten rats each: a food-deprived, a water-deprived and a food and water deprived group. Apparently the rate of weight loss in the three sub-groups did not differ significantly and their data was combined. It was found that running activity was increased as a function of weight loss. Activity was increased to 200% above their baseline rate when they had lost 10% of body weight and so on until at a 40% loss of body weight activity had increased to nearly 1400% above baseline levels.

These/

These studies seem to be consistent with the idea that hunger is an alerting signal leading to increased motor activity in animals.

The evidence from humans is less clear-cut. Bryan and Carlson (1962) failed to demonstrate any differences in spontaneous activity when five men were deprived of food for 99h. However, motor activity in babies has been found to be a function of the hours since they were last fed (Irwin, 1932). The above studies looked at amounts of motor activity integrated over time and it can only be supposed that the increased restlessness associated with hunger also disturbed sleep.

(b) Hunger disturbed sleep

A number of studies have specifically investigated the effects of hunger on sleep. Wada (1922) reported that she found an association between periods of stomach contractions and body movements in sleeping adult humans and children. Body movements during sleep are commonly regarded as an index of less restful and lighter sleep.

The following experiments move out of the realms of normal hunger and into those of chronic starvation and undernutrition and so may be measuring the effect of loss of body mass on sleep.

In/



In a recent study Ruckebusch and Gaujoux (1976a) recorded the sleep/wake patterns of laboratory cats and reported that cats fasted for three days spent less time asleep in the 24h than when they had been allowed to feed normally.

Jacobs and McGinty (1971) analyzed the sleep and wake patterns of rats deprived of food over a prolonged period. They found that the amount of wakefulness in a daily 3h electrophysiological recording (always starting between 9 and 10 a.m.) progressively increased and that the amount of sleep decreased in a reciprocal fashion over the days of deprivation. After 6-11 days of food deprivation sleep had virtually disappeared but re-feeding reversed this effect. This study does suggest that the amount of sleep was reduced by hunger, however only 3h recordings were made and one cannot tell if the normal circadian rhythm of sleeping and waking had been displaced by food deprivation. The authors did say that they had checked the validity of using 3h recordings by undertaking several 24h recordings. Rats have a high metabolic rate, relative to man, and so a week or more of food deprivation resulted in an average loss of body weight of more than 30% and so the disruption of sleep may be due to loss of weight (or depletion of fuel stores). An interesting point is that the most significant effects of starvation on sleep in the above experiment were/

were not seen until some 6-9 days had passed without food, which suggests that the loss of body mass below a critical level may be the important factor for disruption of sleep by wakefulness.

Chronic under-nutrition (and so loss of body tissues) has been reported to be associated with less total sleep and sleep fragmented by wakefulness. In a study of the effects of under-nutrition in Wuppertal between 1946-9 (Russel Davis 1951) it was found that insomnia was a common complaint in ex-prisoners of war and in civilians who had lived on a restricted diet owing to severe rationing of food. Both groups had lost body weight owing to inadequate energy intakes.

Anorexia nervosa patients restrict their food intake to such an extent that they become considerably under-weight and Crisp et al. (1971) have studied their sleep before and after treatment to restore their body weight. They found that after treatment the amount of time spent awake or merely drowsy through the night was significantly reduced. A finding that was later confirmed in another study from the same laboratory (Lacey et al., 1975).

In a study of the sleep of obese patients during weight loss Crisp et al. (1973) found that their patients reported that they slept less as they lost weight on a diet restricted to 500 cal/day and so it may have been the lack of food or the loss of weight that was disrupting sleep.



However, in the Lacey et al. (1975) study the ten anorexia nervosa patients were given approximately the same diet throughout the refeeding period and yet the improvement in sleep paralleled the gains in body weight and, in the study by Crisp et al. (1973) above, the five obese patients, on average, reported that their sleep became progressively shorter as body weight was steadily lost, yet their calorie intake was constant. These studies suggest that losing body weight is associated with less sleep and gaining body weight is associated with sleep of longer duration. Subsequent to their initial findings relating changing body weight to changes in sleep, Crisp and Stonehill (1973) reported an investigation of 375 psychiatric out-patients. Each patient was interviewed by three independent observers. One interviewer made an assessment of the patients' sleep before the illness and of their recent sleep, another interviewer assessed the present and previous body weight. Thereafter a consultant rated the patients' psychiatric status. Correlational analysis showed that gain in body weight was associated with improvement in sleep, and loss of weight was associated with a deterioration in sleep which had become of shorter duration and more broken by waking. The important point was that these associations between change in weight and change in sleep remained when factors such as age, mood and psychiatric diagnosis were partialled out.



(c) Sedative effect of food

It is a common experience to feel sleepy after a large meal and who has not noticed that their pet cat or dog often sleeps after feeding? Many people habitually take a hot milky drink or light snack at bedtime to "help them sleep" and mothers know that a hungry baby will not sleep soundly. Many might dismiss the belief that food can act as a sedative and put it into the same category as the effects of placebo pills in susceptible people. However, in the last few years evidence has accrued that points to there being connections between the gut and the brain, which suggest that food may in fact have a sedating influence. Introduction of milk into the duodenum of cats resulted in drowsiness (shown by EEG spindling) if the animal was active, or in a transition to slow-wave, high-voltage sleep if the cat was already drowsy. The authors, (Fara et al, 1969) also reported that within an hour of the injection of milk into the duodenum there was an increased frequency and duration of REM sleep episodes if the injection was into a sleeping animal. No such effects were found if the milk was injected into the stomach. Subsequent experiments indicated that it was the fat component of milk that was the important factor in these effects for none among water, saline, glucose, lactose or casein elicited the effect, but corn-oil in the duodenum did. The/

The duration of the changes after corn-oil was also found to be proportional to the amount of oil injected (0.5 to 2.0 ml). In a later study Rubinstein and Sonnenschein (1971) again reported that intraduodenal fat (2ml corn oil) led to an increase in total time spent asleep and in the number of episodes and percentage of REM sleep in three cats, during a 3h recording period. However, on close inspection of their report I was unable to see how they arrived at their conclusions. They had also claimed that a single large meal increased the percentage of the 3h recording time, spent asleep and that this was accompanied by an increase in the amount and frequency of REM sleep. This claim was based on a comparison of cats when fed with when they had had no meal for 12h. The unfed animals were monitored electrophysiologically from 9 a.m. to 12 a.m. after 12h of food deprivation to represent the unfed condition. On another day they were exposed to food from 9 a.m. to 1 p.m. after 12h of food deprivation and then recorded from 1 to 4 p.m. I do not doubt that feeding has sleep-promoting effects in cats but this experiment failed to demonstrate it because of poor design. The sleep-wake cycle is a circadian rhythm and so at different times of the 24h there is a greater or lesser tendency to sleep. The above experiment monitored cats in the fed and unfed state at different times of day and so the authors may have contaminated their results by interference from circadian rhythm effects.



The effect of altering the times for feeding on sleep in the rat has been demonstrated by Mouret and Bobillier (1971). The normal pattern in which there was more sleep during the daylight hours than during the dark was found when rats were fed ad libitum or during the dark period only. By contrast rats fed only during the light hours altered the temporal position but not the total amount of slow wave sleep over a number of days, and, more strikingly, the number of REM episodes became more numerous during the dark hours than during the light, and the relative percentage of REM sleep was increased relative to the control rats. These effects were not immediate but took about 2 weeks to become established suggesting gradual readjustment of the sleep-wake rhythm in response to an imposed alteration in the feeding schedule. Similarly, a return to ad libitum feeding reversed the changes in sleep but this took about 2 weeks to be completed. The lighting regime was the same throughout the entire period (light:dark, 12h:12h). Folk (1954) also reported that altering the feeding time from midnight (normal) to noon, in rats kept entirely in darkness, shifted the pattern of running activity from shortly before midnight in the normal group to shortly before noon in the noon fed rats and one assumes that the converse may be true of the sleeping pattern. Interestingly enough, when the rats were/



were illuminated from 6 a.m. to 6 p.m., shifting the feeding period did not shift the activity rhythm, although the author did not record the sleeping pattern.

In this Chapter I suggest in general terms that feeding causes sedation. Although many people do experience post-prandial drowsiness it is usually at bedtime that they specifically eat to aid their sleep. It seems reasonable to predict that the sleep-promoting effects of food are greater at the time of the 24h when the likelihood of being asleep is greatest. An indication that this is the case was alluded to in a letter by Rubinstein (1972), when he said that food in the gut releases the intestinal hormones cholecystokinin (CCK) and secretin (Wang and Grossman, 1951) and that he and his colleagues had found that the intra-venous infusion of CCK into cats was associated with an increase in total sleep during the hour-long infusion (Rubinstein and Sonnenschein, 1971). The interesting point he added (which was not mentioned in their 1971 paper) was that the sedating effect of CCK was dependent on the time of the 24h and the greatest effects were found at the time of the circadian sleep/wake rhythm when sleep was most likely to occur anyway. In contrast CCK infusions during other periods had no detectable/

detectable effect, which suggests that the degree of sedation after food may well depend on the timing of the daily sleeping and waking rhythm.

(d) The effects of nourishment at bedtime on subsequent sleep.

A warm milky drink at bedtime is popularly believed to help you fall asleep more readily and lead to more restful sleep and probably because of this a number of studies have been undertaken over the years to investigate the influence of bedtime eating on sleep. Their various conclusions are contradictory. Some, but not all of the differences are, in retrospect, explainable.

Many years ago Stanley and Tescher (1932) undertook an investigation into the effects on sleep of different types of food eaten at bedtime. Movements during sleep were monitored as an index of the restlessness of sleep. Seven men prisoners were the subjects and each was monitored for 10 nights after each of the following forms of bedtime intake (1) nothing to eat at bedtime (2) 4oz of cake as a carbohydrate snack (3) 4oz egg or meat as a protein snack and (4) 1oz butter on toast as a fatty snack.

The treatment order was not balanced.

The/

The authors reported the mean movements per hour for each subject on each treatment and the grand means for each treatment were -

- (1) Nothing to eat at bedtime 7.89 movements/hour
- (2) Carbohydrate snack 8.56 movements/hour
- (3) Protein snack 9.00 movements/hour
- (4) Fatty snack 8.76 movements/hour

Without any statistical analyses of the results the authors concluded that more restful sleep is had if nothing is eaten on going to bed and that a protein rich snack causes more disturbance than either a fatty or carbohydrate rich snack. However, all seven subjects received the four treatments in the same chronological order and thus seasonal effects cannot be eliminated and so little notice should be taken of the results.

Later Giddings (1934) reported the results of his study of the effects of different forms of food on children's sleep. Body movements were monitored by a device which was an adaptation of a contact breaker and this was set up under each bed in two dormitories of a children's home. Each experiment was carried out over five consecutive nights and involved six boys and six girls. The effects on sleep of five different conditions of bedtime nourishment were studied. He compared the number of body movements after warm water with the number after/





after nothing to eat or drink at bedtime and found no difference. Similarly, there was no significant effect owing to cold water at bedtime compared with either nothing or cold milk at bedtime. Also, a drink of sweetened orangeade had no significant effects and neither did a drink containing 0.6g of caffeine. He reported that after warm milk at bedtime 41.7% of children were less restless, 8.3% had more movements and in 50% there was no change. From this he concluded that "the drinking of 6oz of warm milk at bedtime seems to produce quiet sleep in normal children". Stripped of the percentages he had actually found that 5 children slept better, 1 child slept worse and 6 showed no changes in body movements after warm milk at bedtime, which is not very convincing as evidence for the rather bald statement above.

Giddings also investigated the effects on the number of movements during the children's sleep of (1) a normal evening meal of fruit, cereal or eggs and bread, butter and milk (2) a 'heavy' meal of fruit, meat, vegetables, a dessert and loz of sweets and (3) a light meal of just a slice of bread and butter and a glass of milk. Meals were taken at 1830h and the children retired to bed at 2030h. He found that in 23 out of 24 children motility was increased after the heavy meal. No significant difference was found between the normal and the light meal.

The apparently detrimental effect on sleep of a 'hard to digest' snack at bedtime was also found by Laird and Drexel (1934) in their group of eight young adult men. The quality of sleep was measured by the number of body movements over an 8h sleeping period. Body movements were measured by a mechanical system. Subjects had their sleep monitored nightly over six to eight weeks. On about one third of the nights no bedtime snack was given, on another third the 'easy to digest' snack of milk and cereal was eaten and on the other third of the nights a 'hard to digest' snack, rich in hemicellulose was given. The authors do not mention whether they balanced the order of giving the three treatments over the eight subjects. They found that without exception all subjects had their fewest body movements after a bedtime snack of milk and cereal, the most after the 'hard to digest' supper whereas the number of body movements after no bedtime snack was intermediate between the two.

A similar study in eight children was reported in the above paper. The children were compared with themselves under three different conditions of evening intake (1) their usual evening meal (2) an evening meal based largely on milk and cereal (3) a "hard to digest" meal made up of foods that were slow to digest, producing flatulence or were diuretic. The children retired to bed shortly after their evening meal. Apparently without

without exception the children were more restless after the 'hard to digest' meal than after their usual evening meal and the most peaceful night was achieved after the milk and cereal meal. It might be that a food containing a combination of milk and cereal is more likely to promote restful sleep than other sources of nourishment and indeed this was also reported by Kleitman et al. (1937) in their study of sleep after different types of food at bedtime. The list of foods or drinks taken just prior to going to bed included: one or two sandwiches, made of bread and meat or cheese, an 8 oz. glass of hot milk or cold milk, or hot or cold water and as an example of a proprietary brand of food drink they tested Ovaltine dissolved in milk or water (hot or cold). The Ovaltine was tested at two concentrations of 8 and 14 g per 8 oz glass in both media and at the two temperatures. Many hundreds of nights of sleep were recorded in this experiment to ascertain what type of food (if any) led to more restful sleep. The restfulness of sleep was determined by the number of body movements, expressed as the average motility per hour. Many comparisons were made but none among hot or cold milk, hot or cold water, the lower concentration of Ovaltine in either medium at either temperature or the sandwiches, had any significant effect on sleep motility when compared with sleep after the control condition of no bedtime snack. In contrast the higher concentration of Ovaltine dissolved in hot milk/



milk led to significantly less restless sleep than after the control condition. Analyses of the collective results after the higher concentration of Ovaltine in both media and at both temperatures in comparison with the results after the control condition showed that there was a significant reduction ( $p < 0.01$ ) in motility after the Ovaltine-containing drinks. Similarly when all the results for the higher concentration of Ovaltine in all media were pooled and compared with the results collected from all media without Ovaltine added, a significant reduction ( $p < 0.05$ ) in sleep motility was attributable to the addition of 14g of Ovaltine to the media. In addition their statistical analysis showed that the temperature at which a drink is taken has no effect on subsequent motility during sleep. Ovaltine is a food drink powder based on milk and cereal and so the results of this extensive study again suggest that a milk and cereal combination promotes more restful sleep than other forms of nourishment. However, Hamilton et al. (1966) reported that they found no significant differences between sleep motility after a milk and cereal snack and sleep after nothing to eat at bedtime in 36 male subjects. Their negative results may have arisen partly because the subjects selected to take part in the study were nine middle-age men convalescing from tuberculosis and 27 young monastery students. The authors/

authors did not mention if the patients were being given drugs which might affect their sleep and I also wonder if, during this convalescent period, they may well have been sleeping more soundly to aid the restoration and repair of body tissues lost or damaged by the disease, and therefore the consumption of a bedtime snack might have little effect on sleep that was already sound without any treatment being taken.

The 27 young monastery students also failed to show any effects on their nocturnal motility when the milk and cereal snack was taken at bedtime. Young men on average, sleep so well that there is little room for improvement and this may be the reason for the lack of effect of the snack. It may also be a matter of habit and taking a snack at bedtime may not be the normal pattern in a monastery.

Southwell et al. (1972) also studied the effect on sleep of a milk and cereal food drink (Horlicks) made up in warm milk compared with nothing to eat or 350ml of warm water prior to retiring to bed. Sleep quality was assessed by the number of body movements. The sleeper was filmed by time-lapse cinematography, where a frame was taken automatically every 15 seconds. Body movements were categorized into large and small from the sequence of frames taken of the sleeper. Subjects were allowed/

allowed to sleep under the experimental conditions several times before the results were recorded on two nights for each treatment, in balanced order. There were only four subjects and so the study can only be regarded as a preliminary report. The whole night (1 a.m. to 7 a.m.) results show no convincing difference in the rate of occurrence of large body movements among the three treatments, however they did suggest that Horlicks was associated with a progressive decline in the rate of small body movements, whereas both water or nothing to drink at bedtime led to a progressive increase in the rate of small body movements as the night wore on. All that can be concluded from this study is that there is a suggestion that food in the form of milk and cereal, such as Horlicks, may be better than nothing to eat in reducing the number of small body movements through the night. The major disadvantage of using body movements alone as an index of the restfulness of sleep is that the method cannot discriminate between movements made while asleep and those occurring when a subject is awake. Březinová and Oswald (1972) measured body movements during the night in a group of ten young volunteers and at the same time recorded their sleep electrophysiologically and so were able to exclude body movements during wakefulness from the/



the analysis. The experiment compared the effects of the milk and cereal food drink Horlicks made up in milk with the effects on sleep of an inert yellow capsule. After adaptation on two nights to the laboratory situation, subjects' sleep was actually recorded on eight nights each: four nights when the food drink was taken and four nights when the placebo was taken prior to retiring to bed. Treatment order was balanced across the eight nights. In their group of young subjects they found that the number of body movements in the last three hours of sleep completed by each individual (excluding periods of wakefulness) were fewer after Horlicks at bedtime than after the placebo and this approached statistical significance ( $p < 0.055$ ). No other features of sleep in these young subjects were found to be significantly different. In contrast, when the same experiment was repeated in a group of middle-aged subjects, significant differences in their sleep were found when the nights when Horlicks had been taken at bedtime were compared with the nights on the inert capsule. The authors found that sleep was of longer total duration and less broken by periods of wakefulness after the food drink. The beneficial effect of the food drink significantly increased with serial administration.

To/

To summarize these various studies into the effects of bedtime nutrition on sleep it appears that the general consensus of opinion would be that food taken at bedtime composed of milk and cereal would favour a more restful night than would nothing to eat, or other forms of nourishment. These are, however, tentative conclusions, as not all the studies referred to confirm them. In addition it would appear from the Giddings (1934) and the Laird and Drexel (1934) studies that eating food which was relatively hard to digest would have a detrimental effect and make sleep more restless. It certainly appears that the consumption of food, shortly before retiring to bed, can exert an effect on the quality of subsequent sleep and so it is not surprising that altering the composition of the entire daily intake of food also appears to influence sleep.

(e) Evidence that the specific composition of the diet influences sleep.

Relationships between nutritional status and sleep have been commented on above, e.g. chronic undernutrition as seen in anorexia nervosa patients (Crisp et al., 1971; Lacey et al., 1975) or acute starvation imposed experimentally (MacFadyen et al., 1973) both alter the pattern of sleep. These studies, and others, were primarily investigating/



investigating the effects of either long or short term food deprivation (and associated loss of body mass) and thus a stressful situation for the organism. In the previous section the experimental evidence presented suggested that varying the composition of a meal taken prior to sleep could alter the number of body movements through the night implying that the restful quality of sleep could be influenced, but no indication of any changes in the composition of sleep in terms of the electrophysiological stages of sleep 1,2,3,4 and REM sleep could be measured. If sleep were frequently disrupted, say, by periods of waking, and the total duration of sleep shortened, say, by gastric discomfort then it can be assumed that the pattern of sleep would be disrupted, as repeated interruptions of sleep are known to lower the percentage of the total time asleep which is spent in slow wave (stages 3 and 4) or REM sleep. Recent evidence suggests that the duration and composition of sleep can be influenced by the composition of the daily diet even when the energy intake remains the same.

Fara et al. (1969) found that it was, specifically, the introduction of fat into the duodenum of drowsy cats that led to the transition into slow wave sleep and subsequent augmentation of the amount and frequency of REM/



REM sleep. They failed to find these effects with solutions of glucose, lactose or casein. The energy values of the different types of nourishment were not specified, which contrasts with the study reported by Dallaire and Ruckebusch (1974) where they investigated the effects, on the sleep of three ponies, of two different conditions of nutritional intake (hay v. oats) of approximately equal energy value. Sleep was recorded electrophysiologically on three consecutive nights on each diet. The three ponies were normally maintained on a water and hay schedule and all were first recorded under this dietary regime and this constituted their baseline sleep pattern. After adaptation to the diet of oats, the ponies' sleep was recorded. It was found that when oats were substituted for hay the amount of time spent asleep between 1830h and 0630h increased and this increase was in both slow wave and REM sleep. The diets were not administered in balanced order, but the authors do not think that this unbalanced design contributed substantially to their results as over a week elapsed between the recording periods. They propose a number of possible explanations for these changes. One possibility advanced was that the cellulose content of oats (10%) is lower than that of hay (34%) and the visceral information to the brain may be reduced when oats are eaten, and so activation of the reticular formation is reduced and sleep is more likely. Moreover, /

Moreover, less time is spent feeding under the oats regime and so sensory input is decreased. Finally they suggest that oats may stimulate the secretion of gastrointestinal hormones more than hay, because of the relatively higher concentration of amino acids liberated during digestion. The facilitation of sleep by gastrointestinal hormones has been suggested (e.g. Fara et al. 1969). I will leave the discussion of the possible explanations of the effects of nutrition on sleep to section V of this Chapter.

Another study (Phillips et al., 1975), which investigated the effects of altering the composition of the diet on electrophysiologically-recorded sleep, used eight young men as subjects and diets which were more strictly iso-energetic than the study above. Three diets were compared (1) a 'normal balanced' diet; (2) a high carbohydrate, low fat diet and (3) a low carbohydrate, high fat diet. The amount of protein (75g) was the same in all diets. The experimental design involved two blocks of four consecutive days separated by two weeks. On days 1 and 2 of each block subjects were fed the normal diet (1). Their sleep was recorded electrophysiologically on nights 1 and 2 but only the second night's results were used in the analysis, the first serving as a laboratory adaptation night. During days/



days 3 and 4 one of the experimental diets was fed and on nights 3 and 4 sleep recordings were made. The order of receiving the experimental diets (2) and (3) was balanced over the eight subjects.

Experimental design (Phillips et al., 1975)

Consecutive days	1	2	3	4
	Normal diet		Experimental Diet	
Recordings	Adaptation night	First night recorded	Second night	Third night

Two weeks later the above was repeated with subjects eating the experimental diet (2) or (3) that they had not had in the first part of the experiment. This study design may be criticised in that the order of receiving the experimental diets was balanced but this was not so for the normal diet and hence any conclusions drawn from the comparisons between the control diet and either of the experimental diets must be viewed with caution. In addition the sleep patterns recorded on the nights after either of the experimental diets may have been contaminated by adaptation effects carried over from the first night spent at the sleep laboratory. The amount of REM sleep is particularly likely to be reduced on the first night under laboratory conditions and the rebound increase in REM sleep occurs a night or two later and so with the experimental design above any rebound increase in the amount of REM sleep might occur on/



on the second night actually recorded, namely the first night recorded on either experimental diet. Thus the increase in REM sleep found with both experimental diets may be largely attributable to rebound effects. However, these effects can probably be assumed to affect the recordings on both experimental diets equally and so comparisons between these two diets (2) and (3) are of interest. The low carbohydrate, high fat diet (3) was associated with significantly more slow wave sleep and significantly less REM sleep than the high carbohydrate, low fat diet (2) but the total time spent asleep did not differ. These results suggest that changing the carbohydrate:fat ratio in the diet can alter the proportion of sleep which is spent in slow wave and REM sleep.

An indication that the amount of protein in the diet can influence sleep is suggested by a report by Ruckebusch and Gaujoux (1976b) who increased the dietary nitrogen intake of two sheep by adding urea into the rumen. The sheep were recorded polygraphically for over two months. At variable intervals through this period the nitrogen supplement was given for a number of days. The authors found that when the diet was supplemented with extra nitrogen (but not extra energy) the amount of both NREM and REM sleep duration was increased in the/

the recording period (2000h to 0800h). Whether this effect would operate in non-ruminants is, as yet, an unanswered question.

No consistent pattern of effects of dietary composition can be seen from these few reports and it is difficult to compare studies which have used different types of animals. It does, however, appear that manipulation of the basic composition of the diet within the normal range can alter the duration and/or the amounts of REM and NREM sleep.

A further link between nutrition and sleep can be seen in reports that manipulation of the amount or the composition of the diet can modify the secretion of at least two of the sleep-dependent hormones.

## (II) EVIDENCE THAT NUTRITIONAL STATUS INFLUENCES THE SECRETION OF SLEEP DEPENDENT HORMONES

Feeding patterns, metabolism and the endocrines are intimately inter-related and so it is not surprising that alterations in food intake can influence the secretion of sleep-dependent hormones. The following examples are from experiments carried out in man.

Lipman et al. (1972) reported that the nocturnal elevation of plasma free fatty acids by corn-oil ingestion was associated with an inhibition of the sleep-dependent secretion of growth hormone. The subjects/



subjects were four non-obese young men. Their sleep was recorded electrophysiologically using standard techniques. A cannula was inserted into an arm vein and blood samples were taken at 20 min intervals beginning at 2300h and until one hour after the first period of slow wave sleep. During the period of slow wave sleep blood was sampled at 10 min intervals. Subjects slept under these conditions on two nights, the first served as a control night and on the second they drank 90 ml of corn oil at 2100h and subsequently, when their EEG showed delta activity indicating a progression into slow wave sleep they had an I.V. injection of 50 mg of heparin. The authors analyzed plasma free fatty acids (FFA) and growth hormone (GH) and found that on the control night the mean peak level of FFA during SWS was 500uEq/l, but 2154uEq/l during the experimental night. The mean peak in growth hormone levels was 29.4 ng/ml on the control night and only 2.3 ng/ml on the night when the corn oil had been taken. Unfortunately, the control and experimental nights were not balanced for order and we are not told how many (if any) nights intervened between the two recorded nights. The design appears not to have included an adaptation night to the laboratory, which is even more desirable when subjects have to adapt to both/



both the paraphenalia involved in the electrophysiological recording of sleep and having a cannula in a vein. Nevertheless there was a considerable reduction in the peak level of GH in all four subjects and the results suggest that the sleep-related secretion of GH can be dissociated from the electrical events by inducing elevations in FFAs by a food. It would be interesting to repeat this experiment but continue blood sampling throughout the night to see if the GH peak had been actually suppressed or merely delayed until later in the night.

Another connection between nutritional status and sleep-related GH release was reported by Karacan et al. (1973) who found that acute starvation lasting two days (and two nights) led to a significant elevation in mean peak GH level over baseline levels in a group of 11 young males. The mean baseline (fed) peak GH level was 7.4 ng/ml whereas during the second night of fasting the level was 15.8 ng/ml. Similarly when the mean areas under the curves plotting GH level against time were integrated, the mean area on the night of fasting was significantly greater than on the baseline night. The period of fasting was not only associated with an alteration in the amount of sleep dependent GH secretion but the number of minutes of slow/

slow wave sleep (SWS) was also increased during the period of starvation. The nocturnal secretion of GH is particularly associated with SWS (Sassin et al., 1969a) and this too has been shown to be influenced by starvation. MacFadyen et al. (1973) carried out a more extensive study of the effect of acute starvation on sleep in ten young men. After two adaptation nights in the laboratory, subjects had their sleep recorded on four consecutive nights to establish their baseline sleep patterns when they were eating normally. During the following four days they were starved and their sleep recorded each night, thereafter they were allowed to eat normally again and their sleep was recorded on the four consecutive nights after ceasing to be starved. During the starvation period the mean amount of slow wave sleep (stages 3+4) was significantly raised relative to the period of feeding before and after starvation.

Prolactin is another hormone the nocturnal secretion of which has been found to be dependent on sleep (Sassin et al., 1973) but not associated with any particular electrophysiologically-determined stage of sleep. Recently Hill and Wynder (1976) showed that the source of nourishment in the diet can modify the nocturnal prolactin release. Four young women, who normally consumed a typical Western diet, had their blood sampled at/



at regular intervals through the night (2200h to 0900h). Thereafter they transferred to a vegetarian diet and after two weeks had their blood sampled overnight. Changing to the vegetarian diet and so removing meat from the diet appeared to reduce the nocturnal secretion of prolactin. Although this was obviously only a pilot study, it points to yet another connection between diet and sleep.

Obesity can be seen in simple terms as the net result of a pattern of eating where energy has been consumed in excess of that expended and the excess stored as adipose tissue. In people of normal body weight stimuli such as fasting (Beck et al., 1964), the injection of insulin (Roth et al., 1963) or an infusion of arginine (Burday et al., 1968) provokes a greater rise in plasma hormone level than in obese patients. This difference between people of normal weight and those who are obese is thought to be an adaptation to obesity rather than a cause, because weight gain in normal volunteers can reproduce the effect (Sims and Horton, 1968) and weight loss in obese patients can reverse the suppression (Lessofo et al., 1966; Londono et al., 1969). Obesity also suppresses the sleep-dependent secretion of growth hormone (Kalucy et al., 1976) and it could be predicted that weight loss would restore the normal relationship/



relationship between sleep and nocturnal growth hormone secretion. Obesity is associated with elevated free fatty acids and so the suppression of growth hormone secretion in obese people may be because of the higher levels of free fatty acids. Lipman et al. (1972) found that raising the free fatty acids in people of normal weight suppressed their nocturnal growth hormone secretion. Growth hormone is a lipolytic hormone, which raises the level of free fatty acids and so the level of free fatty acids in the plasma could be part of a negative feedback mechanism to modify growth hormone secretion rate.

Finally, there is some evidence that suggests that growth hormone may influence the amount of REM sleep. In cats I.P. injection of bovine growth hormone during sleep was associated with an elevation of the amount of REM sleep relative to baseline levels in the 3h following the injection. Injection of saline, or thyrotropin did not change the sleep pattern in comparison with the baseline recording (Stern et al., 1975). Similarly, Drucker-Colin et al. (1975b) injected growth hormone into rats and found an increase in the amount of REM sleep. Oswald et al. (1975) studied the effect of injecting 5mg of human growth hormone into ten young human volunteers while they were asleep and found no difference/

difference in the amounts of any of the sleep stages on the nights when growth hormone had been injected compared with those when only saline had been injected. However, for ethical reasons the dose of growth hormone we injected was small in contrast to the high doses injected in the studies done in animals.

This section has been rather a pot pourri of examples where alterations in nutritional status have had effects on the secretion of sleep-dependent hormones and a hint that these hormones may in turn influence sleep, thus giving more evidence for the view that eating and sleeping are interrelated.

The evidence presented in the preceding sections strongly suggests that nutritional status can influence both the pattern of sleep and/or the secretion of sleep dependent hormones and so it would be no surprise to find that changes in sleep can influence food intake.

### (III) EVIDENCE THAT SLEEP CAN INFLUENCE FOOD INTAKE

Spontaneous feeding is dependent on many factors such as the eating habits, nutritional status, hormonal balance, energy metabolism and the psychological state of the animal. In Chapter 1, I outlined how these factors are inextricably related to the circadian rhythm of sleeping and waking and so if changes in the pattern of/



of sleeping can modify metabolism then it is almost inevitable that feeding should also be influenced.

In endocrinology, it is common to speculate about the functions of a gland from the changes following its removal. By analogy, the effects of sleep deprivation are thought to indicate some of the functions of sleep. As I indicated in Chapter 1 sleep deprivation does seem to disturb metabolism and in general terms shift the metabolic balance in favour of catabolic processes, which must, inevitably influence the energy and nutritional balance and so presumably subsequent food intake. Many years ago Manceau and Yorda (1948, cited in Kleitman, 1963) induced continuous wakefulness, in guinea-pigs, by injury at the level of the preoptic and suprachiasmatic zones. Most animals died by the third day, but one survived for 26 days. The interesting thing about this constantly awake animal was that it lost weight despite an increased food intake. This is obviously a rather extreme example but it does link lack of sleep with food intake. A less dramatic manipulation of sleep was carried out by Dement et al. (1967), who deprived cats of REM sleep. The animals were deprived of REM sleep by placing them either on a platform in a watertank (the size of the platform was such that the muscle relaxation associated with REM sleep/



sleep caused them to fall into the water) or by keeping the cats on a slow-moving treadmill for 18 to 22h. For the remaining 2 to 4h of the day the cats were recorded electrophysiologically and allowed to sleep but were awakened every time the recording showed an appearance of REM sleep. The authors found that the 'drive' to eat was enhanced after REM deprivation in that, when hungry, the cats ate faster, would more readily enter water to obtain food or attempt to eat food in which a sparkler was burning than they did when allowed to sleep normally. REM sleep deprivation also increased the amount of food eaten. However, REM sleep deprivation may be stressful (Mendleson et al., 1973) and so it could be said that the effects on food intake were non-specific. Evidence that REM sleep may in fact be related to food intake comes from a study of the patterns of sleep and spontaneous feeding in cats (Siegel, 1975). He found that the amount of REM sleep in a 12h period was an accurate predictor of the amount of food eaten in the subsequent 12h period. The correlation between min of REM sleep and amount of food eaten was negative and so this finding is compatible with those of Dement et al. (1967) in that it would be predicted that REM deprivation would be associated with increased food intake. Later in this thesis I shall present data linking human REM sleep and body weight.

Finally, further evidence for a link between nutritional status and sleep comes from a variety of pathological/

pathological conditions where a disorder of feeding is associated with an abnormal pattern of sleep.

(IV) SOME EXAMPLES OF DISORDERS OF FEEDING  
ASSOCIATED WITH DISORDERS OF SLEEP

Throughout the literature there are reports of patients who have experienced episodes lasting days or weeks where sleep filled most of the 24h of the day. During brief periods of awakening the patients would eat excessively. Critchley and Hoffman (1942) named this the "Kleine-Levin" syndrome in deference to two of the authors who were among the first to report cases of excessive sleep associated with over-eating (Kleine, 1925; Levin, 1936). Later Critchley (1962) described this syndrome as "recurring episodes of undue sleepiness lasting several days associated with an inordinate intake of food". The patients often apparently appear quite normal between attacks and are not always overweight. The latter is in contrast to the so called Pickwickian syndrome which in most, but not all patients, is characterized by an extreme degree of over eating and consequent gross obesity (Burwell et al., 1956). The patients suffer impaired respiration owing to the excessive amounts of adipose tissue and oro-pharyngeal spasm during sleep and during the day they tend to repeatedly fall asleep. The nocturnal sleep pattern is one of frequent apneic periods terminated by irregular snorts, with the EEG then showing the appearance of arousal, and consequently their sleep/



sleep pattern is abnormal with most of the night spent in stages 1 and 2, with reduced amounts of slow wave and paradoxical sleep. Weight loss does sometimes improve the situation.

Idiopathic narcolepsy is a condition where patients have recurrent attacks of overwhelming sleepiness through the day. Patients are particularly vulnerable when bored and the environment monotonous. The periods of daytime sleep are usually relatively brief lasting some 10 to 15 min. The striking characteristic of this syndrome is that they rapidly pass into REM sleep following sleep onset (Rechtschaffen et al., 1963), which is not a feature of normal sleep where the appearance of REM sleep is delayed for about an hour following sleep onset.

The first narcoleptic attack in a patient can often be associated in time with a recent gain in body weight and so this syndrome may also be related to alterations in feeding pattern and/or metabolism.

Excessive post-prandial drowsiness and sleep attacks during meals have been reported (e.g. Zarcone, 1973). Bell et al. (1975) surveyed the diet histories of their narcoleptic patients and found a higher incidence of unusual eating patterns and cravings for specific foods than in a group of normals. Significant differences/



differences of interest between their narcoleptics and normals were: the high incidence of frequent, post-prandial sleepiness, the eating of both daytime and bedtime snacks, eating during the night and a craving for sweets and milk. Also of interest was that the narcoleptic group were significantly heavier than the ideal maximum body weight for their height than the group of normals.

The three broadly defined syndromes referred to above have the common feature that pathological sleepiness is associated (in many of the cases), with eating to excess and frequently with obesity as well. The converse situation is seen in anorexia nervosa patients at the times when they are chronically undernourished and severely underweight. Crisp (1967) drew attention to the poor sleep of these patients and suggested that their insomnia was not a symptom of anxiety but was largely due to the nutritional disturbance. The poor sleep was particularly in the later night and awaking very early in the morning was common. Subsequent research suggested that restoration of body mass was the main factor associated with improvement in sleep and not changes in mood (Crisp and Stonehill, 1970). In a further report changes in subjective ratings of sleep, measured nocturnal motility, psychiatric status and body weight, were measured before and/

and after refeeding ten anorexia nervosa patients (Crisp and Stonehill, 1971). Analysis of the results showed that treatment led to a statistically significant increase in body weight and that the patients' assessment of sleep duration was significantly greater. There was a tendency for sleep to be rated as less broken, for the delay to sleep onset to be shorter and for the final awakening in the morning to be estimated as later. Nocturnal motility was found to be significantly reduced after weight gain. Correlational analysis, among the variables measured, showed that weight gain was significantly associated with a later time for awakening in the morning. Changes in weight or the various measures of sleep did not correlate significantly with the changes in the M.H.Q. (Middlesex Hospital Questionnaire) or E.P.I. (Eysenck Personality Index) scores used to assess psychiatric status before and after treatment.

In another report Crisp et al. (1971) studied the sleep of anorexia nervosa patients before and after treatment, but this time sleep was recorded electrophysiologically. They found that after refeeding for six to 12 weeks the time spent awake or in a drowsy state through the night was significantly reduced. More recently, from the same laboratory, another study was reported which further confirmed that improvement in/

in sleep in anorexia nervosa patients was closely related to restoration of body weight (Lacey et al., 1975). So there seems to be little doubt that it is change in nutritional status and associated alterations in body weight that are primarily responsible for the changes in sleep seen in these patients.

To summarize this section it certainly appears that there are pathological conditions in which patterns of sleep are related to nutritional status, such that over-eating and or overweight are associated with increased amounts of sleep and that the severe weight loss and undernutrition of anorexia nervosa patients are associated with sleep that is fragmented and of shorter duration.



(V) HOW CAN FEEDING INFLUENCE SLEEP?

I have presented evidence that, at least in animals, hunger is associated with motor restlessness. Lack of food, however, cannot be separated from weight loss when it is prolonged over days, and chronic weight loss in humans and animals reduces the time spent asleep. On the other hand, feeding seems to have a sedating action and weight gain is associated with an increase in the amount of sleep.

In this section I will put forward a number of possible explanations for the sedating effect of food intake and although they are put under separate headings this does not imply that they are mutually exclusive. The ingestion of any food is likely to initiate multiple and interacting effects on the central nervous system by several routes, including (a) direct neural connections between the gut and the brain (b) stimulate the release of hormones such as insulin and the apparently neuro-active gastrointestinal hormones such as cholecystikinin and (c) supply precursors for neurotransmitter synthesis.

(a) Direct neural connections between gut and brain.

Experiments in animals have shown that feeding is associated with synchronization and increased voltage in the electroencephalogram and that these changes are very rapid and are functionally indicative of decreased arousal, /

arousal, higher states of arousal being associated with low voltage and desynchronized electrical brain rhythms. Hockman (1964) reported that the electrocorticogram of fasted rats had a predominance of low voltage, high frequency activity, whereas fed animals showed a marked increase in high voltage slow waves. Food consumption in cats was also found to be associated with high voltage electrocortical activity (Hess et al., 1953; Anokhin, 1961). Sterman et al. (1963) trained cats to press a lever to obtain a reward of a small amount of liquid food. In cats deprived of food obtaining the reward was simultaneously associated with a synchronization of the EEG. Later, Sterman and Wyrwicka (1967) and Marcynzynski et al. (1968) obtained similar results. In the latter experiment food-deprived cats, implanted with electrodes in the cortex, had to press a lever to obtain a reward of milk. During the consumption of the reward their electrocorticogram displayed bursts of relatively large amplitude spindle activity in the parieto-occipital region. The authors reported that this post-reinforcement synchronization was indistinguishable from sleep-spindle electrocortical activity recorded from the same area in satiated cats and they concluded that there is a functional overlap between reward centres and hypnogenic (synchronizing) influences. They interpret their results in terms of appetite/



appetite gratification similar to other consummatory activities such as copulation which in rabbits has been shown to produce electrocortical synchronization (Sawyer and Kawakami, 1959) and so presumably the mechanism involves a direct neural connection.

Rosen et al. (1971) compared the electrocortico-gram of rats deprived of food for 22h with that of rats allowed to eat after a comparable period of food deprivation. They found that satiated rats had more high voltage, slow waves in their electrocorticogram than the hungry rats and that transfusion of blood from a satiated rat to a fasted rat led to electrocortical synchronization, the latter suggesting that a humoral factor is also involved.

Rats appear to be able rapidly to recognize that nourishment has entered the upper gastrointestinal tract (Puerto et al., 1976). This was shown by an experiment where rats were given a choice of two differently-flavoured non-nutrient drinks. As an animal drank one of the flavoured liquids, a nourishing liquid was pumped into its stomach through an implanted tube, but when the rat drank the other liquid no nutrient was injected. The rats were found rapidly to choose (within 10 min) the flavoured drink paired with nourishment, but only when the nourishment was in the form/



form of pre-digested milk. Saline, fresh milk, glucose or glucose plus digestive juice did not have that effect, suggesting that stomach distention alone was not responsible for the effect. The rapidity of the effect and specificity for pre-digested milk rather precludes the likelihood of a raised blood level of an absorbed nutrient being the signal, and points to either a direct neural link between the gut and the brain, or the rapid secretion of a gastrointestinal hormone which then acts on the central nervous system.

It would appear from the evidence presented in the section above that the very rapid electrocortical synchronization seen in food-deprived cats when they receive a food reward must involve a neural connection between the digestive track and the brain or it could conceivably involve the sensory organs. The blood transfusion experiment<sup>and</sup> where rats appeared specifically to recognize when pre-digested milk had been injected into the stomach, both point to a change in the blood level of a humoral factor influencing the central nervous system.

(b) Release of neuroactive gastrointestinal hormones.

The gut is an endocrine organ and its hormones have multiple effects. These hormones include gastrin, secretin,/

secretin, cholecystokinin, bradykinin and enteroglucagon. At present cholecystokinin is the hormone most clearly implicated in the sedating effect of food.

Fara et al. (1969) found that intraduodenal fat had a sedating effect on the EEG pattern of cats and because fat in the duodenum releases cholecystokinin (CCK) they tested the effect of intravenous infusion of CCK. Infusion into awake but drowsy cats induced high-voltage sleep suggesting that the sedating effect of fat was, at least in part, mediated by CCK. A further experiment (Rubinstein and Sonnenschien, 1971) involved infusions of CCK and secretin (another hormone the release of which is stimulated by intraduodenal fat). From the text of this paper it is not clear what had been found but in a later publication Rubinstein (1972) said that in the 1971 report they had found that during the one-hour infusion of the intestinal hormones, especially CCK, there were long-lasting episodes of slow wave and REM sleep. There is, however, no indication if this is more or less than the normal for the time of day when the recording was made. The possibility that gastrointestinal hormones do play a part in the sedating effect of food remains and awaits confirmation.

(c) Supplying/



(c) Supplying precursors for neurotransmitter synthesis

Brain serotonergic (5HT) neurones have been implicated in the mechanisms underlying sleep (e.g. Jouvet, 1967) and 5HT may also antagonize the systems promoting waking (Koella and Czicman, 1966). It is thus of great interest that the levels and synthesis of serotonin in the mammalian brain have been shown to depend on the availability of the precursor amino acid l-tryptophan and so depend ultimately on the diet.

Experiments have shown that the brains of rats chronically fed tryptophan-deficient diets contained much less serotonin than normally fed animals (Gal and Drewes, 1962), however deficiency of any essential amino acid can inhibit protein synthesis and so the lowered levels of serotonin found could have been due to reduced levels of the enzymes in the serotonin synthetic pathway. Other studies found that feeding animals normal diets supplemented with tryptophan raised brain serotonin levels (Green et al., 1962) and so taken together these experiments suggested that the diet could influence brain serotonin levels.

A great deal of subsequent research was undertaken to elucidate by what mechanism changes in the diet could influence brain serotonin levels.

Changes/



Changes in brain tryptophan were shown to modify the rate of brain serotonin synthesis (Jéquier et al., 1967). The locus of control was found to be the first step in the metabolic pathway between tryptophan and serotonin, namely the hydroxylation of tryptophan. Evidence suggests that it is precursor availability and not end-product inhibition which modifies the activity of tryptophan hydroxylase. In vitro studies of this enzyme have shown that physiological levels of serotonin do not appear to suppress its activity (Jacoby et al., 1975). The possibility that precursor availability might be the important factor was suggested by finding that the  $K_m$  of the enzyme tryptophan hydroxylase for tryptophan was  $3 \times 10^{-4} M$  (Jéquier et al., 1969) which is considerably greater than the tryptophan concentration in whole brain:  $2$  to  $5 \times 10^{-5} M$  (Fernstrom and Wurtman, 1971a). This rather large difference between the  $K_m$  and the brain concentration would hardly allow fine control of hydroxylase activity so the  $K_m$  of  $5 \times 10^{-5} M$  calculated using the enzymes natural cofactor biopterin seems more likely (Kaufman, 1974). Nevertheless with either  $K_m$  tryptophan hydroxylase is not normally saturated with its substrate in vivo. Thus fluctuations in brain tryptophan level can alter the degree of saturation, consequently the rate of tryptophan hydroxylation and so the rate of serotonin synthesis./

synthesis. From the point of view of feeding influencing brain serotonin, having established that the rate of brain serotonin synthesis is vulnerable to changes in brain tryptophan concentration, the next question is how can plasma levels of tryptophan influence brain levels of tryptophan?

The investigation of this question has been actively pursued over the years and a number of interesting points have arisen:

- (1) The level of brain <sup>r</sup>tryptophan (and so brain serotonin) depends on the plasma level of tryptophan. This was shown by injecting rats with physiological amounts of tryptophan (Fernstrom and Wurtman, 1971a).
- (2) A high protein diet was found to raise plasma tryptophan levels but paradoxically brain tryptophan and serotonin levels were unaffected (Fernstrom et al., 1973). It was realized that the plasma tryptophan level alone is not a reliable indicator of brain levels, but instead it is the ratio of the plasma tryptophan level to that of the other neutral amino acids which compete with tryptophan for the common transport carrier across the blood-brain barrier (Fernstrom and Wurtman, 1972; Pérez-Cruet et al., 1974).
- (3) Injection of insulin into fasted rats rapidly elevated plasma tryptophan, brain tryptophan and serotonin/



serotonin (Fernstrom and Wurtman, 1971b). In humans plasma tryptophan is little affected following an injection of insulin (Lipsett et al., 1973) however the level of the competing amino acids falls (Wurtman, 1970) and so the plasma level of tryptophan rises in relation to the level of the other neutral amino acids in plasma and so presumably brain tryptophan is elevated.

(4) Rats fasted overnight and then fed with only carbohydrate and fat were found to have elevated plasma tryptophan, brain tryptophan and serotonin levels when compared with fasted controls (Fernstrom and Wurtman, 1971b) and the carbohydrate-induced elevation of brain serotonin was later shown to be due to an increased rate of serotonin synthesis (Colmenares et al., 1975).

While the evidence above clearly demonstrates that the composition of the diet can modify brain tryptophan and serotonin levels it does not establish whether there are corresponding changes in the amounts of the amine released into synapses. In other words, can behaviour such as sleeping, sexual activity, pain sensitivity and feeding, which are thought to depend on serotonergic neurones, be changed by dietary manipulation? There is a little evidence that some of these behaviours can be modified.

Corn is deficient in tryptophan and rats fed on it have been shown to have lowered levels of brain tryptophan/



tryptophan and serotonin when compared with well-nourished rats (Fernstrom and Wurtman, 1971c). The brain serotonin level of corn-fed rats could be restored to normal by injection of l-tryptophan (Fernstrom and Hirsch, 1975). It has been found that the pain sensitivity threshold of the well-nourished rats was higher than the corn-fed rats, a difference that could be reversed by tryptophan supplementation of the deficient diet or by transferring the corn-fed rats to a casein diet (Lytle et al., 1975, Messing et al., 1976).

A few studies have investigated the effects of oral tryptophan in humans. Oswald et al. (1964) reported that it reduced the latency to the first appearance of REM sleep and Hartmann et al. (1974) have claimed that subjects fall asleep more quickly after tryptophan (administered in a milk shake!) given 20 min before retiring to bed. It has also been suggested (Wyatt et al., 1970) that tryptophan can enhance total sleep time by increasing non REM sleep. So it seems that there is, as yet, no clear picture as to what effect tryptophan has on sleep.

In this Section V, I have put forward a variety of mechanisms whereby feeding could have a sedative effect. These proposed mechanisms are not mutually exclusive/

exclusive and would undoubtedly interact, e.g. the gastrointestinal hormones CCK, secretin and glucagon are known to stimulate insulin secretion which in turn can influence brain tryptophan levels. In addition the operation of any of these mechanisms will depend on the rhythms that pervade life. Virtually every physiological, psychological and biochemical function investigated has shown rhythmicity e.g. the effectiveness and toxicity of a drug can be modified by the time of the 24h when it is administered (Walker, 1974). The circadian fluctuations in the levels of biogenic amines (Friedman and Walker, 1968) and the activity of hepatic enzymes metabolizing drugs (Nair et al., 1970; Chedid and Nair, 1972) must play a part in this.

Plasma amino acid levels are subject to 24h rhythms (Wurtman, 1970) and the fate of ingested tryptophan depends on whether it is taken at 9 a.m. or 9 p.m. (Rapoport and Beisel, 1968). Pain sensitivity (Reinberg et al., 1967) and the level of cortical arousal similarly exhibit rhythms (Lavie et al., 1975).

CHAPTER 3

AN INVESTIGATION INTO THE EFFECTS OF A PLACEBO, OF  
HORLICKS AND OF NITRAZEPAM ON SLEEP

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## CHAPTER 3

### SUMMARY

Ten middle-aged subjects had their sleep recorded electrophysiologically before, during and after taking Horlicks nightly for ten weeks and before, during and after taking nitrazepam 5mg nightly for ten weeks.

Nitrazepam significantly improved sleep throughout the period of administration, whereas Horlicks at bedtime had no effect on sleep.

A comparison between sleep after a placebo pill with sleep after nothing at bedtime revealed no differences.

## INTRODUCTION

In a study comparing sleep after an inert capsule with sleep after a hot, milk cereal food drink (Horlicks) Březinová and Oswald (1972) found that the food drink at bedtime was associated with sleep of longer total duration and with less interruption by periods of wakefulness, in a group of eight middle-aged volunteers. They also reported that the improvement in sleep associated with the food drink was most obvious in the second half of the night and that the beneficial effects increased over repeated administration.

The effects of Horlicks on sleep were deemed weak, by these investigators, in comparison with those found with hypnotic drugs, however, hypnotic drugs often become less effective when taken for long periods of time and their withdrawal can lead to considerable disruption of sleep for many nights. Horlicks had been found to become more effective with serial administration and the authors speculated that Horlicks might be comparable to an hypnotic drug in efficacy in long-term use.

Nitrazepam is one of the most commonly prescribed hypnotics and it was selected to test the speculation that with chronic use the bedtime food drink would become/

become more effective in improving sleep and that nitrazepam would become less effective with long-term use.

In addition, a study to investigate the power of suggestion associated with a placebo treatment was incorporated into the experimental design, because of the criticism (Iverson and Mackay, 1972) that the effectiveness of Horlicks in improving sleep could be largely attributable to a placebo effect, the suggestion of sleep-promoting properties associated with Horlicks through advertisements.

For reasons which I hope will become clear when the results are seen, I have divided the presentation of the experiment into five parts. First, a general description of the experimental method, and thereafter treating the investigations into the effects of a placebo, Horlicks and nitrazepam as three separate reports and finally an overview of the entire experiment.



PART (1): GENERAL DESCRIPTION OF EXPERIMENT

(a) Subjects and Experimental Design

Ten volunteers took part in this cross-over study between the food drink, Horlicks and the benzodiazepine, nitrazepam 5mg. There were six women and four men of mean age 57y (range 41-62y). They had taken no drugs in the preceding months and were asked not to take any drugs other than those given by us, and to consume no alcohol.

Subjects attended the laboratory in pairs differing from each other in the treatment they received, and thus treatment order was balanced. They each slept in a quiet and comfortable bedroom on a total of 58 nights spread over 38 weeks according to the experimental design:

Weeks 1 and 2	2 adaptation nights 6 baseline nights
Weeks 5 and 6	1 adaptation night 6 early treatment nights
Weeks 7,8, 9 and 10	treatment continued at home
Weeks 11 and 12	1 adaptation night 6 late treatment nights
Weeks 13 and 14	treatment continued at home
Weeks 15 and 16	1 adaptation night 6 withdrawal nights

The treatment was taken every night, from the first early treatment night to the night preceding the recording of the first withdrawal night. Thus every subject/

subject took the treatment for ten weeks.

Six weeks later subjects repeated the above schedule on the alternative treatment. Treatments were administered 30 min before lights-out (approximately 2230h to 0715h).

The days of the week that subjects came to the sleep laboratory were not exactly the same for each period but their 7/8 attendances were evenly spread over each two week period.

On half the baseline nights and in balanced order each subject was given a pink placebo pill. They were given a written statement which said that the pill was a mild sleeping pill.

The food drink was made from 32g of Horlicks powder mixed with 250ml of hot milk.

#### (b) Recording of sleep

On all nights the ~~parieto-occipital~~ electroencephalogram, bipolar eye-movements and submental muscle tone were recorded.

The 580 electrophysiological recordings of sleep were coded and read "blind" as to the experimental condition, and categorized into the different stages of sleep and wakefulness according to the criteria of Rechtschaffen and Kales (1968). Using this raw data a computer programme was used which calculated the time it took a subject to fall asleep, the total amount of time/

time slept and the time from sleep onset to the first appearance of REM sleep. The number of min spent in each stage of sleep in the accumulation of each successive hour of sleep was also determined.

Wakefulness was treated as intruding into sleep and any wakefulness through the night is presented in terms of the amount of waking that occurred in the accumulation of each successive hour of sleep. Thus, if 20 min of waking had intruded into the first hour of sleep, then it had actually taken 80 min to achieve the first 60 min of sleep.

The number of transitions to wakefulness plus the number of transitions to stage 1 that occurred in each successive hour of sleep was also calculated as this gives an index of the restlessness of sleep.

The results of all ten subjects for each night were averaged for each of the stages of sleep and wakefulness by collecting together all the data from the first, second, to the seventh hour of sleep and dividing each hourly total by ten. If any subject slept for less than seven hours the denominator was reduced.

Incomplete hours of sleep were treated as follows:-

If, for example, a subject slept for 4h 40min then his sleep data for this incomplete fifth hour of sleep was included in the fifth hour total of all subjects, but when/



when the mean for the fifth hour was calculated, the denominator would be 9.5 instead of ten. If several subjects had slept for less than five complete hours, then the divisor was calculated by adding the number of complete fifth hours plus all the decimal fractions and then dividing the grand total minutes of the particular sleep measure, in that fifth hour, by the calculated denominator.

PART (2): EFFECT OF A PLACEBO ON SLEEP

INTRODUCTION

There have been remarkably few investigations into the effects of a placebo on sleep. This is surprising in view of the fact that many studies involve the administration of a treatment whose nature cannot be disguised, and with which subjects may associate an effect. Also, there is pressure on doctors to prescribe fewer sleeping pills and many must wonder if an inert substitute might be effective through suggestion alone.

Kales et al. (1971) compared the effect of a placebo with no-treatment on the sleep of eight young men, who had complaints about their sleep. No significant differences were found between the five nights on each treatment for such measures as the time it took to fall asleep, the total time spent asleep, the distribution of the various sleep stages, or the subjective ratings of the quality of sleep. The subjects had been told that they might be given a 'dummy' pill at some time during the experiment.

Davis and Hartmann (1973) recorded sleep electrophysiologically in two groups of nine subjects. One group comprised young males and the other middle-aged women. No significant differences were found in the total time asleep or in the time to fall asleep between the means of three placebo and three no-treatment nights.

In a later experiment involving 12 young men, Hartmann and Cravens (1973a) compared the mean of nine all-night sleep recordings collected at intervals through a 28-day period of daily placebo administration with the mean of three preceding no-treatment nights. The authors reported a rather tenuous connection between placebo administration and an increased amount of REM sleep. They also reported an increase in REM sleep following 'withdrawal' of the placebo, but this may have been an artifact of the unbalanced design.

The present investigation into the effects of a placebo on sleep differs from those referred to above in that our ten middle-aged subjects were told that the inert pill was a mild sleeping pill which would have a beneficial effect on their sleep and hence more specifically investigated the power of suggestion.



## METHODS

As mentioned in the general description of the experiment (Part 1) this study was carried out on the baseline nights, which preceded both the period of Horlicks and the period of nitrazepam administration.

### (a) Experimental Design

Subjects were given a written statement, before the experiment began, which read, "You will be given a mild sleeping pill, it will help to make your sleep more restful without causing any hangover". An inert, pink pill was administered, 30 min before lights-out, on half the recorded nights. Subjects attended the laboratory in pairs, always differing from each other as to whom received the pill on any one night.

The experiment, out of necessity, was divided into two halves, separated by 21 weeks. During each period, subjects had their sleep recorded electro-physiologically on eight nights, of which the first two served for adaptation and were discarded. Thus each of the ten subjects received, in balanced order, the inert pill on six nights and nothing on the other six experimental nights.

### (b) Statistical Analysis

Correlated t-tests (Ferguson, 1959) were used to compare/

compare the 60 placebo nights with the 60 no-treatment nights using each subject's mean under either condition. Friedman's analysis of variance (Siegel, 1956) was used to compare the mean latency to the first appearance of REM sleep when the placebo had been taken with the nights when nothing had been given.

### RESULTS

The overnight recordings of sleep revealed no significant differences between the 60 placebo pill nights and the 60 no-treatment nights. Table 3.1 shows the lack of influence of the placebo on the accumulation of wakefulness that intervened during the night's sleep and this was true throughout the night (Figure 3.1). Similarly, the accumulated min of intervening wakefulness combined with the min of stage 1 (drowsiness) were unchanged by placebo administration (Figure 3.2).

The amounts of stage 1, stage 2, stages 3 + 4, and REM sleep (Table 3.2) were so obviously unaffected that statistical analyses were not undertaken. The mean total sleep duration, the time taken to fall asleep and REM sleep latency were also unaffected (Table 3.3). The number of times that sleep was disrupted by waking or periods of drowsiness (stage 1) were combined and also found to be unaffected (Figure 3.3)

NOTE:/

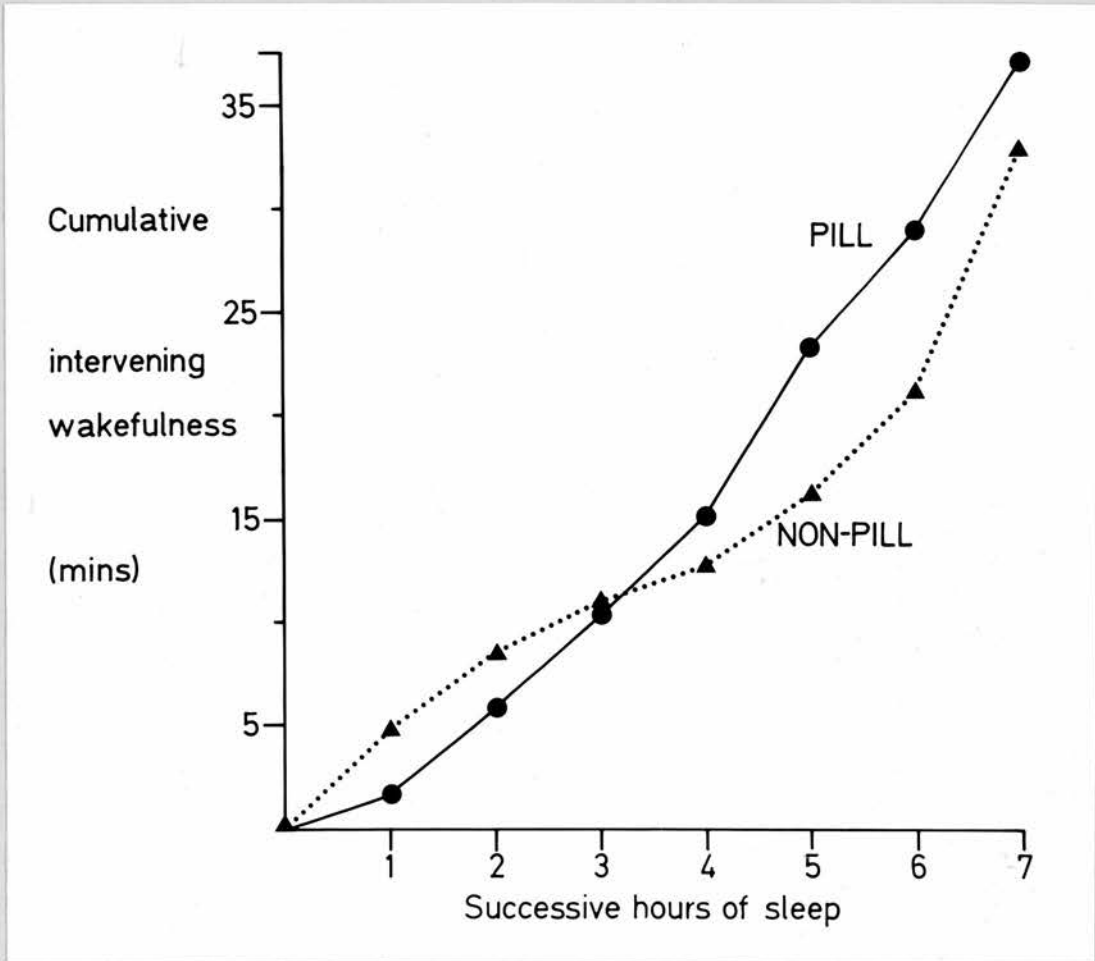


FIGURE 3.1 Mean cumulative min of wakefulness interrupting the first 7h of sleep of 10 middle-aged subjects.

The placebo pill was taken on 6 nights and no treatment (Non-pill) on 6 nights.

Pill nights v. no pill nights:  $t = 0.90$ ,  $df = 9$  (n.s.)



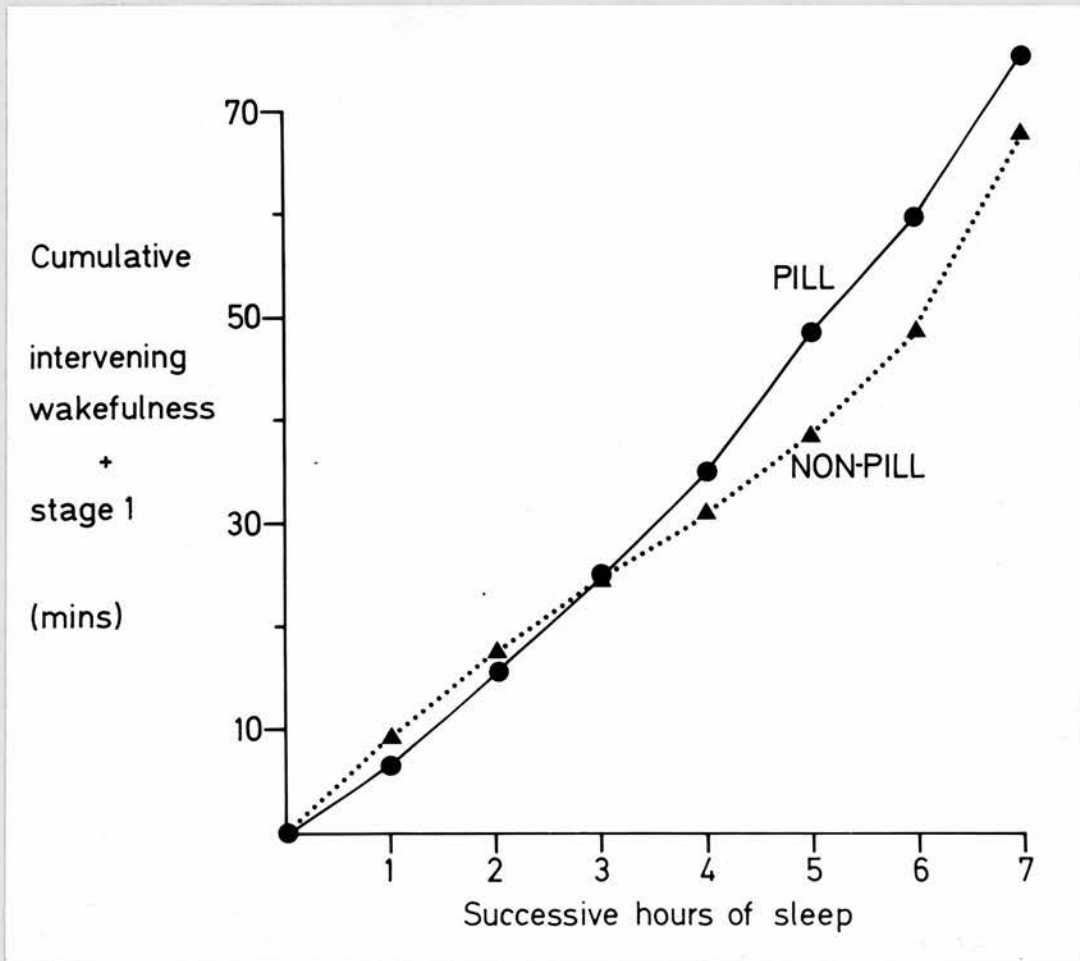


FIGURE 3.2 Mean cumulative min of intervening wakefulness combined with the mean cumulative min of stage 1 (drowsiness) occurring in the first 7h of sleep of 10 middle-aged subjects.

The placebo pill was taken on 6 nights and no-treatment (Non-pill) on 6 nights.

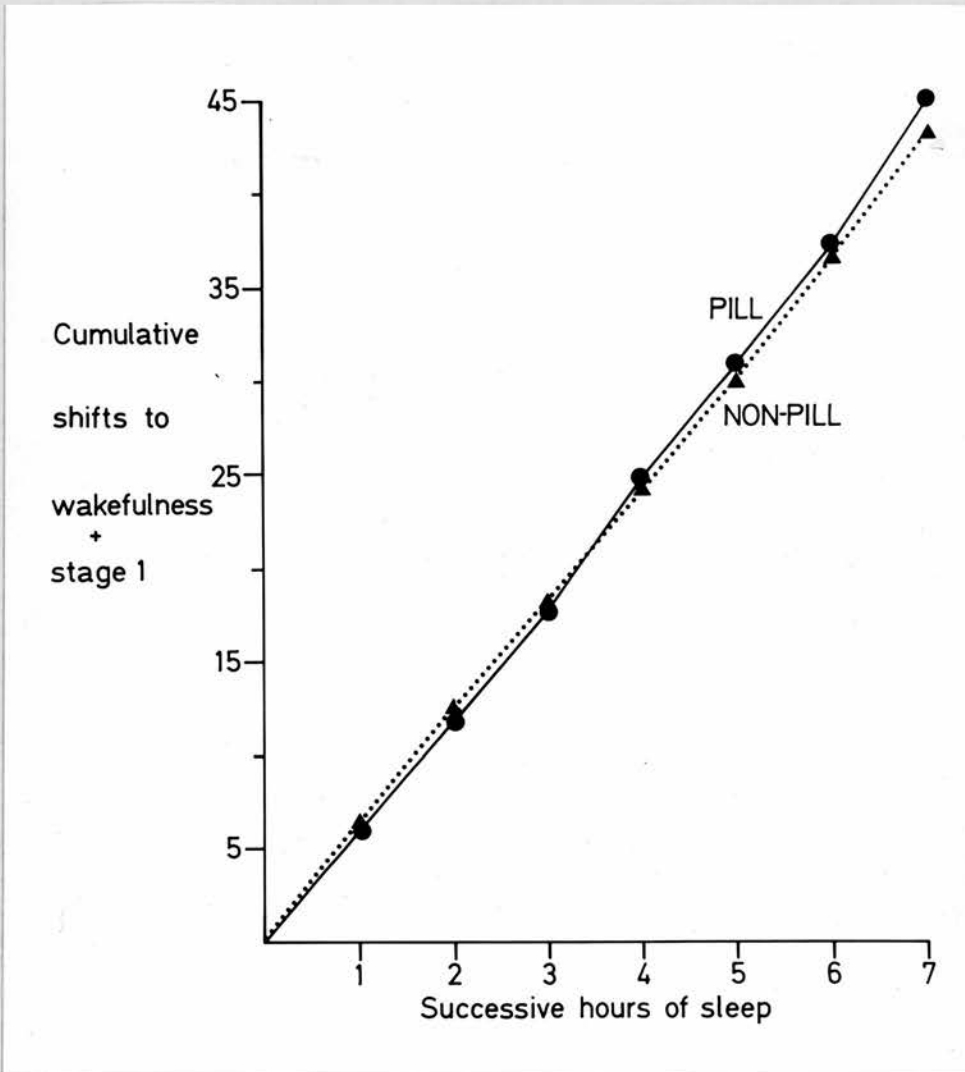


FIGURE 3.3 Mean number of times that sleep was disrupted by periods of wakefulness combined with the mean number of shifts to stage 1 (drowsiness) in the first 7h of sleep of 10 middle-aged subjects.

The placebo pill was taken on 6 nights and no-treatment (Non-pill) on 6 nights.

NOTE: The slight discrepancy between the mean total min of intervening wakefulness accumulated in the first 7h of sleep shown in Table 3.1 when compared with Table 3.2 is a consequence of the different methods used to calculate the means. The means shown in Table 3.2 were calculated as described in section (b) of Part 1 of this chapter, whereas the values listed in Table 3.1 were obtained by summing each individual subject's mean total min of wakefulness in the accumulation of the first 7h of sleep.



## DISCUSSION

The sleep of older people is frequently broken by periods of wakefulness (Feinberg et al., 1967; Agnew et al., 1967; Kales et al., 1967b; Williams et al., 1972; Březinová, 1975) and hence more likely to show any beneficial effects of a treatment. Their sleep also appears to be more vulnerable to any adverse influence, such as the disruption of sleep following caffeine ingestion shortly before going to bed (Březinová, 1974a), whereas the sleep of younger subjects is affected less (Gresham et al. 1963). Had the negative result in the present investigation been found in young subjects it could be said that younger people usually sleep so well that there is little room for improvement. In an earlier study of the food drink 'Horlicks' no significant effect was found in EEG recorded sleep of young people, whereas the sleep of a group of older subjects, similar to those studied here, was significantly less broken after the food drink when compared with sleep after an inert pill (Březinová and Oswald, 1972).

Any experiment which investigates the value of a treatment whose identity cannot be concealed is faced with the problem of how large a part suggestion may play in the results. In the present investigation subjects/

subjects were specifically told that their sleep would be improved and yet this was not reflected in the results.

To conclude, the results of this study offer no support for the supposition that the beneficial effects of hypnotics or bedtime food on sleep are attributable to suggestion, nor do they give evidence for any belief that the sleep of middle-aged people would be substantially altered by prescribing a placebo.

TABLE 3.1. EFFECT OF A PLACEBO ON SLEEP

Individual subjects<sup>2</sup> mean total min spent awake in the accumulation of the first 7 h of sleep. Each value for each of 10 subjects is the mean of 6 nights.

Subjects	Mean min	
	Placebo pill nights	No-treatment nights
BB	49.5	31.1
MC	73.2	28.3
JG	26.2	54.4
GH	20.5	54.7
GJ	14.5	11.2
DJ	2.5	20.2
RMcd	93.3	29.8
JR	23.2	26.8
MS	7.1	2.8
MT	64.5	61.4
Mean±S.D.	37.5±30.8	32.1±19.3

t-test for paired observations (2-tailed)

Placebo v. No-treatment nights:  $t = 1.02$ ,  $df = 9$  (n.s.)



TABLE 3.2. EFFECT OF A PLACEBO ON SLEEP

Mean total min spent in each of the sleep stages, wakefulness and shifts of sleep stage to awake and to stage 1 in the accumulation of the first 7 h of sleep. Each value is the mean of 60 subject nights: 10 subjects each recorded for 6 nights under each condition.

	Mean min	
	Placebo pill nights	No-treatment nights
Intervening wakefulness	36.9	32.8
Intervening wakefulness plus stage 1	74.9	67.2
stage 2	214.5	213.6
stages (3 + 4)	82.4	84.4
stage REM sleep	84.2	86.8
<hr/>		
Number of shifts to awake and to stage 1	45.0	43.0

TABLE 3.3. EFFECT OF A PLACEBO ON SLEEP

Whole night measures. Each value is the mean of 60 subject nights: 10 subjects each recorded for 6 nights under each condition.

	Mean $\text{min} \pm \text{S.D.}$		Statistical analysis t-tests for paired observations
	Placebo pill nights	No-treatment nights	
Total time asleep	453.2 $\pm$ 36.2	445.7 $\pm$ 32.1	t=0.62, df=9, (n.s.)
Latency to first onset of sleep	24.9 $\pm$ 12.2	21.9 $\pm$ 13.3	t=0.78, df=9, (n.s.)
Latency from sleep onset to the first * REM period	79.8 $\pm$ 22.0	81.2 $\pm$ 24.3	$\chi^2_r = 0.4$ , df=1, (n.s.)

\*non-parametric test (Friedman's analysis of variance) used because data not normally distributed

### PART (3): EFFECT OF HORLICKS ON SLEEP

#### METHODS

Subjects attended the sleep laboratory on 29 nights according to the experimental design described in Part 1 of this chapter. On 24 of these nights electrophysiological recordings were made and comprised six pre-food drink baseline nights, six early food drink, six late food drink nights and six withdrawal nights. The four conditions were spread over 16 weeks for each of the ten subjects.

#### RESULTS

No significant differences were found on the objective measures of sleep among the four conditions. Table 3.4 summarizes the analyses of the means of the whole-night measures: total time asleep, latency to sleep onset and latency from the first onset of sleep to the first appearance of REM sleep. Table 3.5 shows the individual subject's mean total time asleep under the four conditions and Table 3.6 shows the same for the total min of intervening wakefulness occurring in the first 7h of accumulated sleep. Table 3.7 summarizes the mean totals of the 7h of sleep for the different sleep stages, intervening wakefulness and the combined shifts of sleep stage to wakefulness and to stage 1. It was unnecessary to apply statistical tests to confirm these statements, as it was obvious from the group means that there were no significant differences.



NOTE: The small discrepancies between the mean total min of intervening wakefulness in the first 7h of sleep shown in Table 3.6 compared with Table 3.7 are due to the difference between the methods of calculating the means. The values shown in Table 3.6 were arrived at by calculating the mean number of min of intervening wakefulness in the first 7h of sleep for each subject under each condition. Thereafter the mean min over the ten subjects was calculated for each condition. Whereas the data shown in Table 3.7 was calculated by averaging the min of intervening wakefulness occurring in the first hour of sleep for all ten subjects and similarly for the second, third and so on up to the seventh hour of accumulated sleep. Then the seven hourly means for each night were added together. Thereafter the six 7h means for the baseline period were averaged, as were the six means for the early and late drink and withdrawal periods.

## DISCUSSION

The complete absence of effect of Horlicks at bedtime came as a surprise at the time. In retrospect, however, it will be found not so surprising. The volunteers in this experiment had been given no instructions to abstain from food and drink in the evening which contrasts with the restriction on eating and drinking after 1900h in the earlier study comparing sleep after Horlicks with sleep after an inert capsule (Březinová and Oswald, 1972) No dietary restriction had been imposed because it had been intended that the comparisons between the bedtime food drink and the drug should be as near to the "at home" conditions as possible.

I would now predict that, had there been a restriction imposed on eating and drinking in the evening, I would have obtained different results.

Some of the subjects in the present study, were definitely taking a snack shortly before coming to the sleep laboratory during the baseline period and commented that they would feel hungry during the night without it! The lack of any significant differences under these circumstances between the subjects' sleep during the pre-food drink baseline and the subsequent periods of food drink administration suggests that the food drink Horlicks might have no special sleep-promoting powers other than its basic nutritional composition and that the/

the superiority of Horlicks over a placebo capsule, found by Březinová and Oswald (1972), was largely attributable to the detrimental effects on sleep of the lack of bedtime nourishment when subjects had had nothing to eat or drink after 1900h. If that were the case then one would predict that other types of bedtime nourishment would be comparable to Horlicks when compared with a placebo capsule, with the proviso that subjects curtail their food intake in the early evening.

The question of whether the composition of a bedtime snack has any bearing on its effects on subsequent sleep is dealt with in Chapter 5 of this thesis.



TABLE 3.4. EFFECT OF HORLICKS ON SLEEP

Whole night measures. Each value is the mean of 60 subject nights:  
10 subjects each recorded for 6 nights under each condition.

	Mean min±S.D.			
	Baseline pre-drink	Early drink	Late drink	Withdrawal
Total time asleep	452.0±27.8	452.6±35.0	452.8±38.3	451.5±31.7
Latency to sleep onset	24.0±13.1	19.8±11.4	20.4±11.5	20.7±13.9
Latency from sleep onset to the first REM period	79.4±21.4	69.5±12.6	79.5±15.0	76.2±21.7

No significant differences among conditions

TABLE 3.5. EFFECT OF HORLICKS ON SLEEP

Mean total min asleep for each individual subject. Each value for each of 10 subjects is the mean of 6 nights.

Subjects	Mean total min asleep			
	Baseline pre-drink	Early drink	Late drink	Withdrawal
BB	405.6	411.6	388.8	394.3
MC	443.7	407.8	411.1	441.9
JG	443.3	427.5	481.0	453.5
GH	436.9	479.0	479.4	480.2
GJ	505.7	515.1	509.9	494.5
DJ	488.6	489.3	485.9	493.7
RMCD	441.9	462.8	467.3	442.7
JR	453.4	458.9	445.5	442.7
MS	457.4	430.0	421.8	419.1
MT	443.0	443.5	437.1	452.6
Mean±S.D.	452.0±27.8	452.6±35.0	452.8±38.3	451.5±31.7

No significant differences among conditions

TABLE 3.6. EFFECT OF HORLICKS ON SLEEP

Mean min of intervening wakefulness occurring in the first 7 h of accumulated sleep. Each value for each of 10 subjects is the mean of 6 nights.

Subjects	Mean min intervening wake in 1st 7 h sleep			
	Baseline pre-drink	Early drink	Late drink	Withdrawal
BB	41.1	53.5	26.8	67.3
MC	25.2	41.8	66.5	42.1
JG	55.9	49.8	19.7	33.2
GH	40.2	15.4	10.9	15.4
GJ	9.1	2.4	4.7	21.2
DJ	21.6	14.5	20.5	19.4
RMCD	45.7	26.3	32.6	54.8
JR	30.9	26.1	33.8	28.2
MS	5.6	24.7	55.2	25.9
MT	55.7	56.0	59.6	32.9
Mean±S.D.	33.1±17.7	31.1±18.3	33.0±21.0	34.0±16.4

No significant differences among conditions



TABLE 3.7. EFFECT OF HORLICKS ON SLEEP.

Mean total min spent in each of the sleep stages, wakefulness and shifts of sleep stage to awake and to stage 1 in the accumulation of the first 7h of sleep. Each value is the mean of 60 subject nights: 10 subjects each recorded for 6 nights under each condition.

	Mean min			
	Baseline pre-drink	Early drink	Late drink	With- drawal
Intervening wakefulness	34.2	30.7	33.4	34.2
Stage 1	36.9	37.6	38.5	37.1
Intervening wakefulness plus Stage 1	71.1	*69.4	*71.8	71.3
Stage 2	214.3	213.7	218.6	210.6
Stages (3 + 4)	84.1	88.5	76.3	85.7
Stage REM sleep	84.7	80.2	86.6	86.6
<hr/>				
Number of shifts of sleep stage to awake and Stage 1	43.9	44.5	42.9	44.1

\*NOTE: slight discrepancies in totals because of rounding error.

PART (4): EFFECT OF NITRAZEPAM ON SLEEP

INTRODUCTION

The benzodiazepine nitrazepam was selected for the comparison of efficacy between chronic use of an hypnotic and long-term administration of the food drink Horlicks because it is the most commonly prescribed sleeping pill in Britain and thus a study of its effectiveness over many weeks of use would be of interest.

Insomnia, especially in older people, appears to be a common problem (Dunnell and Cartwright, 1972) and hypnotic drugs are frequently taken over long periods of time and yet there are few reports investigating the effects of their long-term administration. 'Insomnia' is a blanket term which covers several different aspects of inadequate sleep, which can occur singly or in combination. A patient may have difficulty in falling asleep at the beginning of the night, wake repeatedly through the sleep period or awaken very early in the morning. Electrophysiological recording of sleep can tell us accurately how long it took a person to fall asleep, how often and for how long they were awake and how many minutes of sleep they accumulated through the night. In addition, recordings of sleep reveal any changes in a subject's usual number of min and chacteristic distribution of the different stages of sleep through the night, which may occur when a drug has been taken.

## METHODS

### (a) Experimental Design

Subjects attended the sleep laboratory on 29 nights according to the experimental design described in Part 1 of this chapter. On 24 of these nights electrophysiological recordings were made: six baseline nights, six early drug, six late drug and six withdrawal nights spread over 16 weeks for each of the ten subjects. Subjects took 5mg of nitrazepam nightly for ten weeks.

The first night on the drug and the first night after coming off the drug were recorded for every subject.

### (b) Statistical Analysis

It is a perennial problem in this type of investigation to find a statistical test which can satisfactorily be applied, because treatment order cannot be balanced and the different periods of the study are not independent of each other. For example, on the first night without the active drug after several weeks of use (first withdrawal night), the effects of the drug are often still present and so the withdrawal period is contaminated by the persistence of the drug or its metabolites in the body. Averaging the results over the withdrawal period can conceal the sequence of events that frequently occur when the active drug is withdrawn. Similarly, measurements made/



made after chronic use of a drug are not independent of the measurements made during the period of initial administration of the drug, as the former evolves from the latter.

The questions we wanted to answer were:-

(i) Do the patterns of sleep differ among the four conditions of the experiment, namely, pre-drug baseline; early drug; late drug and drug withdrawal?

(ii) When the drug is first taken are there any effects on sleep?

(iii) Do these effects persist?

(iv) When the drug is withdrawn do the sleep patterns of the subjects return to those found during the pre-drug baseline period?

I attempted to analyse these questions statistically:

(i) By using the non-parametric Friedman's analysis of variance by ranks (Siegel, 1956). I used this ranking method to eliminate the effects attributable to inter-individual differences, as I only wanted to see if there were any consistent differences across the four conditions.

(ii) to (iv) By using t-tests for paired observations (Ferguson, 1959) between the appropriate pairs of experimental conditions. A one-tailed level of significance was employed, when a prior prediction had been made e.g. it was predicted that nitrazepam would significantly improve sleep and that its withdrawal would lead to sleep that was more broken by wakefulness and of shorter total duration.

## RESULTS

Table 3.8 shows a summary of the mean total min of each of the sleep stages, wakefulness and the number of shifts of sleep stage to awake and to stage 1 accumulated in the first 7h of sleep. Inspection of these group means revealed which measures would merit statistical analysis.

(a) Effects of nitrazepam on induction, duration and brokenness of sleep.

Subjects slept significantly longer while taking the drug (Table 3.9). This improvement in sleep was maintained throughout the period of drug administration as comparison of the early and late drug results illustrates. However, on withdrawal from the drug, the time spent asleep was significantly shorter than recorded during the baseline period, before the drug had been taken.

The interruption of sleep by periods of wakefulness was reduced by the drug, throughout the period of administration, with no apparent tolerance as there was no significant difference between the early and late drug periods. Withdrawal from the drug increased intervening wakefulness, when compared with baseline as Figure 3.4 shows. Withdrawal from the drug affected some subjects' sleep/

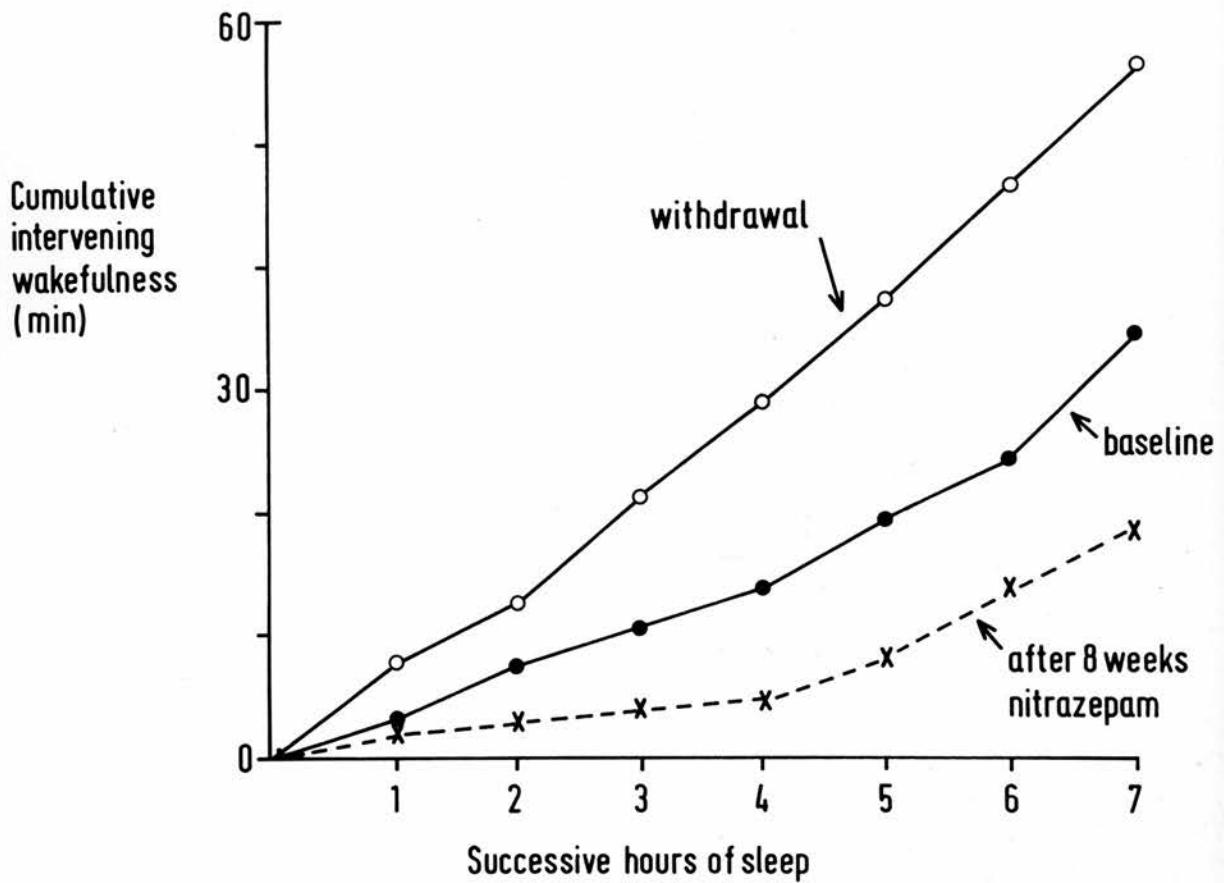


FIGURE 3.4 Mean cumulative min of intervening wakefulness occurring in the first 7h of sleep of 10 middle-aged subjects.

Six nights were recorded under each condition for every subject.

Statistical analysis (where applicable) and a measure of the inter-individual variance in Table 3.10.



sleep profoundly, in one case total sleep time was reduced to 42 min, and, because of this, statistical assessment of these particular data using individual means was impracticable. Table 3.10 shows the individual means and group means for the total amount of intervening wakefulness in the first 7h of sleep for the baseline, early drug and late drug periods and how wakefulness interrupting sleep was significantly reduced during both the early and late drug periods. The early and late drug periods did not differ significantly.

A statistical assessment of the effect on wakefulness of withdrawing the drug was obtained by comparing the total wakefulness occurring between first falling asleep and the end of the recording in the morning. The recordings lasted the same length of time and therefore the measure does give a reliable indication of the amount of waking occurring after subjects had first fallen asleep. This amount of time awake was significantly higher during the withdrawal period and considerably higher two nights after the last dose of nitrazepam had been taken (Figure 3.5 + Table 3.11). All subjects had their first night, without the drug, recorded. The 'second' withdrawal night recorded was for some subjects the second night without the drug but for others it was actually the third night without the drug. The mean number of nights without/

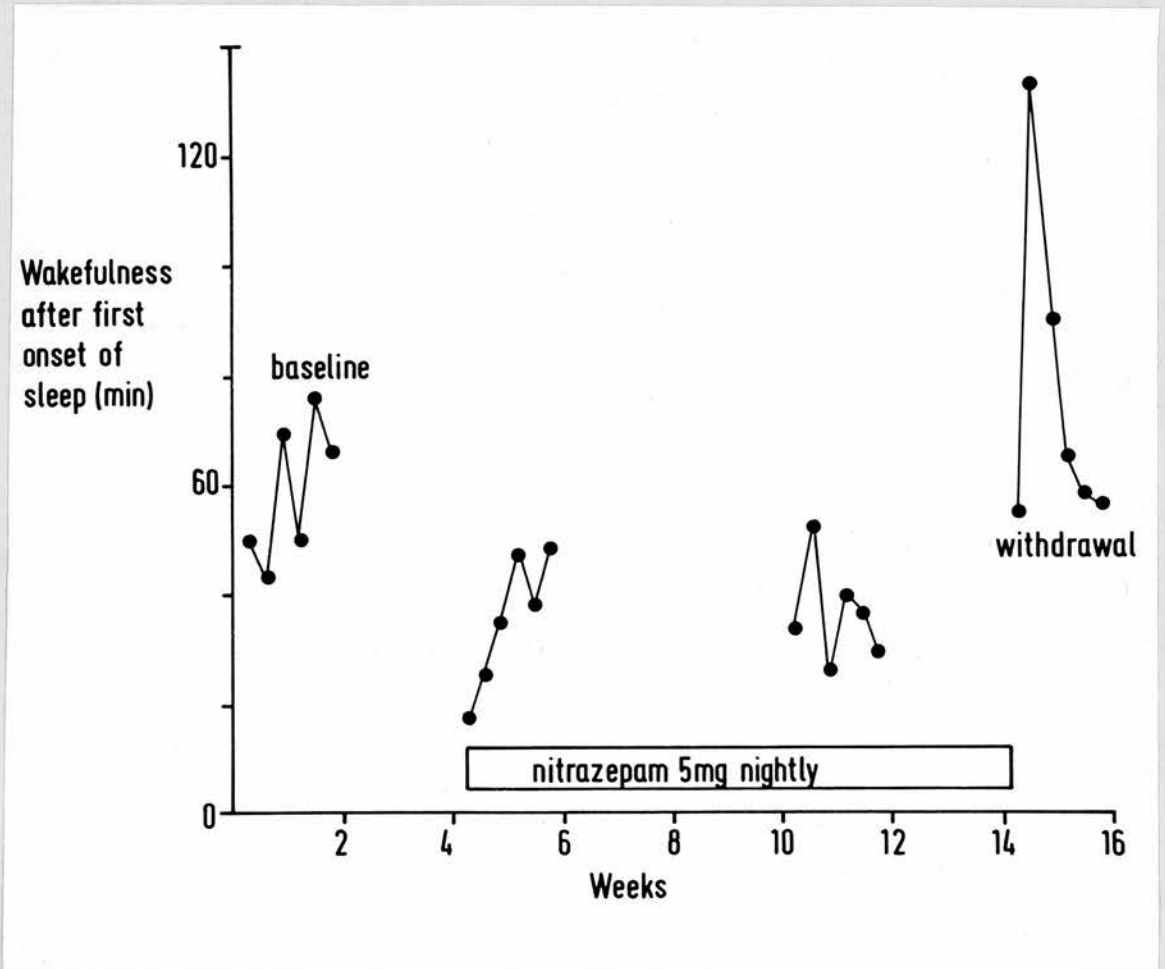


FIGURE 3.5 Mean total wakefulness recorded after the first onset of sleep in 10 middle-aged subjects.

Each point on the graph is the mean of the 10 subjects.

Statistical analysis and a measure of the inter-individual variance in Table 3.11.

without the drug, when the 'second' withdrawal night was recorded was 2.3 nights.

The time it took subjects to fall asleep was not significantly changed (Table 3.12).

(b) Effect of nitrazepam on amount and distribution of REM sleep.

Table 3.13 shows that the total minutes of REM sleep accumulated in the first 7h of sleep was significantly reduced during the early drug period when compared with the baseline mean whereas the late drug mean was not significantly different from the baseline mean. The reduction in REM sleep during the early drug period occurred almost exclusively within the first 3h of sleep (Table 3.14) and this significant early night reduction was still present in the late drug period. However, by the late drug period a significant increase in REM sleep had appeared in the later night, hours 4 to 7 of sleep, (Table 3.15) suggesting the development of a later night rebound in REM sleep. Withdrawal of the drug returned the distribution of REM sleep between the early and late night, to baseline values.

The latency from sleep onset to the first appearance of REM sleep did not differ significantly among the four periods of the study. This measure is not normally distributed and so only the non-parametric test was employed (Table 3.16).



(c) Effect of nitrazepam on amount of slow-wave sleep (SWS)

The mean duration of SWS (stages 3+4) accumulated in the first 6h of sleep (Table 3.17) was significantly reduced during early drug and during late drug administration when compared with baseline levels. The mean values recorded during the late drug period were significantly lower than those of the early drug period. Withdrawal of the drug returned values to baseline values, without a rebound increase over baseline, in the nights immediately following withdrawal.

## DISCUSSION

Normal ageing is associated with a reduction of sleep duration and more interruption by periods of waking (Agnew et al., 1967; Kales et al., 1967b; Feinberg et al., 1967; Williams et al., 1972; Brezinová, 1975). The subjects involved in our study were of an older age group and so more representative of those who complain of inadequate sleep.

The overnight recordings of sleep were sufficiently long (8.75h) to allow any increase in sleep duration to be detected and reveal any changes in the distribution of sleep stages which might occur towards the end of the period of sleep. The latter is particularly true of REM sleep which occurs predominantly in the later part of the night and thus if the duration of the sleep period was curtailed information about changes in this sleep stage could be lost.

Nitrazepam proved effective in reducing the amount of wakefulness interrupting sleep and sleep duration was increased. The maintenance of nitrazepam's action for over two months of use is paralleled by flurazepam when studied during four weeks of administration and contrasts with the ineffectiveness of pentobarbital revealed after only two weeks of use (Kales et al., 1975). Glutethimide 500mg, 1000mg chloral hydrate (Kales et al., 1970; 1970b) 100mg secobarbital (Kales et al., 1976a) and triazolam 0.5mg/

0.5mg (Kales et al., 1976b) nightly have also been shown to become less effective over a two-week period of administration. The longer period of drug-taking in our study was thus even more likely to reveal any tolerance effects. The fact that it did not suggests that nitrazepam might be a choice for long-term use.

The mean min from lights-out to sleep onset ranged from 8.8 min to 48.4 min (mean 22.8 min). This relatively short latency to sleep onset may account for the lack of effect of the drug on the induction of sleep. In patients who have difficulty in falling asleep a reduction might well have been found.

Nitrazepam was found to reduce the amount of REM sleep in the first 3h of sleep and during chronic administration a late-night REM sleep rebound developed, suggesting that the initial reduction of REM sleep had some adverse consequences to which the central nervous system had to adapt. It has yet to be elucidated if distortion of the normal sleep pattern has any deleterious effects and whether a reduction in the electrophysiologically recorded min of a sleep stage can be taken to mean that its underlying function has been suppressed.

The within-night rebound in min of REM sleep during protracted use of hypnotics has been previously reported for/



for barbiturates (Kales et al., 1970c) and for the benzodiazepine flunidazepam (Oswald et al., 1973). The lack of a REM sleep rebound following withdrawal of nitrazepam contrasts with that found with larger doses (Oswald and Priest, 1965). Rebound increases in the min of REM sleep recorded, whether as a later night rebound during a long-term use or following withdrawal, does suggest that some necessary process has been diminished by the drug and that the rebound constitutes some compensatory restoration of that process.

The lack of effect of nitrazepam on REM latency may be due to the relatively low dose 5mg used, for a higher dose has been shown to lengthen REM latency (Haider and Oswald, 1971). Similarly, flurazepam 30mg was reported to lengthen REM latency (Kales et al., 1975).

Nitrazepam caused a progressive decline of slow wave sleep (stages 3+4) as has been reported during chronic use of other benzodiazepines, e.g. flurazepam (Kales et al., 1970c, 1971, 1975), chlordiazepoxide (Hartmann and Cravens, 1973b), diazepam (Fisher et al., 1973; Kales and Scharf, 1973), flunidazepam (Oswald et al., 1973), fosazepam (Allen and Oswald, 1976) and triazolam (Kales et al., 1976b).

The/

The lack of a rebound increase in slow wave sleep (SWS) following withdrawal from the drug suggests that, although the electrophysiological appearance of SWS was reduced the underlying function of SWS may not have been impaired.

The poor sleep following withdrawal of nitrazepam and other hypnotics must tend to perpetuate their consumption.

Patients trying to give up their hypnotics should be reassured that the disrupted sleep, which will last for several nights after stopping the drug, is a temporary consequence of withdrawal from the drug and that their sleep will improve over time.

TABLE 3.8. EFFECT OF NITRAZEPAM ON SLEEP

Mean total min in the first 7 h of sleep for objective measures of sleep and wakefulness. Each value is the mean of 60 subject nights: 10 subjects each recorded for 6 nights under each condition.

	Mean min			
	Baseline pre-drug	Early drug	Late drug	Withdrawal
Intervening wakefulness	35.1	20.9	18.9	56.1
Stage 1	37.2	31.0	33.4	40.2
Stage 2	211.7	249.5	250.9	213.9
Stages (3+4)	82.8	64.2	52.4	79.9
Stage REM	86.8	75.3	84.6	86.0
<hr/>				
Mean number of shifts of sleep stage to awake and to stage 1 combined	44.4	38.6	38.9	47.1

Note: All these results were obtained by averaging the minutes of each sleep measure achieved by the subjects in the first, second, etc. hour of sleep. Thereafter the means of the first, second and so on up to the seventh hour of sleep were added together for each of the 24 nights. Thus the totals differ slightly from Tables 3.10 and 3.13.



TABLE 3.9. EFFECT OF NITRAZEPAM ON SLEEP

Mean total min spent asleep. Each value for each of 10 subjects is the mean of 6 nights.

Subjects	Mean total min asleep			
	Baseline pre-drug	Early drug	Late drug	Withdrawal
BB	419.8	424.8	418.7	376.9
MC	423.2	466.2	450.4	422.7
JG	446.1	465.1	472.9	417.3
GH	470.3	479.7	490.4	468.4
GJ	494.2	496.7	496.2	477.1
DJ	507.5	487.1	504.4	461.9
RMCD	443.0	485.9	464.0	457.4
JR	444.8	472.1	465.8	453.9
MS	407.1	499.0	486.9	371.6
MT	413.3	433.8	441.3	379.6
Mean	446.9	471.0	469.1	428.7
<sup>†</sup> S.D.	<sup>†</sup> 34.1	<sup>†</sup> 24.9	<sup>†</sup> 26.8	<sup>†</sup> 40.8

#### Statistical analysis

- (a) Friedman's analysis of variance to test overall significance of differences among conditions.

$$\chi^2_r = 20.04, df = 3, p < 0.001.$$

- (b) t-tests for paired observations (1-tailed)

baseline v. early drug,  $t = 2.50$ ,  $df = 9$ ,  $p < 0.025$

baseline v. late drug,  $t = 2.97$ ,  $df = 9$ ,  $p < 0.01$

baseline v. withdrawal,  $t = 2.61$ ,  $df = 9$ ,  $p < 0.025$

early drug v. late drug,  $t = 0.48$ ,  $df = 9$  (n.s.) 2-tailed

TABLE 3.10. EFFECT OF NITRAZEPAM ON SLEEP

Mean total min of intervening wakefulness occurring in the first 7 h of accumulated sleep. Each value for each of 10 subjects is the mean of 6 nights.

Mean min intervening wake in 1st 7 h sleep				
Subjects	Baseline pre-drug	Early drug	Late drug	Withdrawal
BB	37.7	28.5	67.1	
MC	71.2	27.0	23.0	
JG	25.0	41.1	15.3	
GH	32.6	7.8	9.8	
GJ	16.7	10.3	10.1	Insufficient data
DJ	1.2	7.7	0.9	
RMCD	72.2	26.0	7.4	
JR	20.0	9.2	25.5	
MS	5.3	1.0	1.1	
MT	69.4	49.8	30.2	
Mean	35.1	20.8	19.0	
$\pm$ S.D.	$\pm 27.0$	$\pm 16.2$	$\pm 19.6$	

t-tests for paired observations (1-tailed)

baseline v. early drug,  $t = 2.26$ ,  $df = 9$ ,  $p < 0.05$

baseline v. late drug,  $t = 1.83$ ,  $df = 9$ ,  $p < 0.05$

early drug v. late drug,  $t = 0.30$ ,  $df = 9$  (n.s.)



TABLE 3.11. EFFECT OF NITRAZEPAM ON SLEEP.

Mean total min of wakefulness occurring after first falling asleep and until the recording ended. Each value for each of 10 subjects is the mean of 6 nights.

Subjects	Mean total min of wakefulness			
	Baseline pre-drug	Early drug	Late drug	Withdrawal
BB	84.4	77.7	83.6	117.7
MC	68.8	39.4	46.8	84.1
JG	71.3	49.0	40.6	96.2
GH	39.2	10.5	15.8	15.4
GJ	34.9	28.0	23.6	42.8
DJ	12.6	27.5	12.6	58.7
RMCD	74.6	28.7	46.9	52.4
JR	34.5	16.9	28.8	29.4
MS	78.1	7.3	9.6	137.2
MT	97.8	73.1	58.1	125.3
Mean	59.6	35.8	36.6	75.9
<sup>+</sup> S.D.	<sup>+</sup> 27.3	<sup>+</sup> 24.3	<sup>+</sup> 23.2	<sup>+</sup> 42.4

#### Statistical analysis

(a) Friedman's analysis of variance

$$\chi^2_r = 19.17, df = 3, p < 0.001$$

(b) t-tests for paired observations (1-tailed)

baseline v. early drug,  $t = 3.24$ ,  $df = 9$ ,  $p < 0.01$

baseline v. late drug,  $t = 3.50$ ,  $df = 9$ ,  $p < 0.005$

baseline v. withdrawal,  $t = 1.87$ ,  $df = 9$ ,  $p < 0.05$

early drug v. late drug,  $t = 0.24$ ,  $df = 9$  (n.s.)



TABLE 3.12. EFFECT OF NITRAZEPAM ON SLEEP

The latency to the first onset of sleep (min). Each value for each of 10 subjects is the mean of 6 nights.

Subjects	Mean min to sleep onset			
	Baseline pre-drug	Early drug	Late drug	Withdrawal
BB	18.5	21.0	20.3	26.5
MC	37.7	24.9	29.2	21.9
JG	8.8	12.4	14.3	12.5
GH	19.0	31.6	18.9	42.0
GJ	9.2	10.6	13.1	18.8
DJ	9.0	10.8	9.5	8.0
RMCD	16.7	19.2	23.8	21.4
JR	48.4	39.3	33.1	45.4
MS	37.2	14.3	19.8	18.2
MT	23.9	20.5	30.3	30.4
Mean	22.8	20.5	21.2	24.5
$\pm$ S.D.	$\pm$ 13.9	$\pm$ 9.4	$\pm$ 7.8	$\pm$ 12.0

Friedman's analysis of variance

$$\chi^2_r = 2.28, df = 3, (n.s.)$$

TABLE 3.13. EFFECT OF NITRAZEPAM ON SLEEP

Mean total min of stage REM sleep accumulated in the first 7 h of sleep. Each value for each of 10 subjects is the mean of 6 nights.

Mean min REM sleep in 1st 7 h of sleep				
Subjects	Baseline pre-drug	Early drug	Late drug	Withdrawal
BB	85.3	80.6	69.3	83.8
MC	106.9	96.4	100.5	102.3
JG	90.3	79.8	88.1	95.3
GH	91.6	63.7	67.3	102.6
GJ	94.7	88.2	91.8	79.7
DJ	94.6	87.5	110.1	97.1
RMCD	58.2	57.3	58.6	59.8
JR	99.6	76.6	94.7	78.5
MS	71.5	65.6	82.5	89.6
MT	58.8	52.5	78.1	46.6
Mean	85.2	74.8	84.1	83.5
± S.D.	± 16.8	± 14.5	± 16.1	± 18.4

#### Statistical analysis

##### (a) Friedman's analysis of variance

$$\chi^2_r = 11.88, df = 3, p < 0.01$$

##### (b) t-tests for paired observations (2-tailed)

baseline v. early drug,  $t = 3.84$ ,  $df = 9$ ,  $p < 0.01$

baseline v. late drug,  $t = 0.25$ ,  $df = 9$ , (n.s.)

baseline v. withdrawal,  $t = 0.43$ ,  $df = 9$ , (n.s.)

early drug v. late drug,  $t = 2.21$ ,  $df = 9$ , (n.s.)

TABLE 3.14. EFFECT OF NITRAZEPAM ON SLEEP

Mean total min of stage REM sleep accumulated in the first 3 h of sleep. Each value for each of 10 subjects is the mean of 6 nights.

Mean min of REM sleep in 1st 3 h of sleep				
Subjects	Baseline pre-drug	Early drug	Late drug	Withdrawal
BB	31.1	8.8	10.9	23.4
MC	43.5	24.2	23.9	35.1
JG	27.8	24.3	22.3	32.2
GH	35.8	12.1	12.6	28.4
GJ	27.1	22.5	18.5	27.9
DJ	33.8	28.1	37.3	39.0
RMCD	17.0	12.7	10.3	13.9
JR	19.9	15.9	22.1	25.2
MS	15.6	10.9	21.0	26.3
MT	10.8	3.4	7.4	13.5
Mean	26.2	16.3	18.6	26.5
<sup>+</sup> S.D.	<sup>+</sup> 10.3	<sup>+</sup> 8.1	<sup>+</sup> 8.8	<sup>+</sup> 8.2

#### Statistical analysis

##### (a) Friedman's analysis of variance

$$\chi^2_r = 18.84, df = 3, p < 0.001$$

##### (b) t-tests for paired observations (2-tailed)

baseline v. early drug,  $t = 3.80$ ,  $df = 9$ ,  $p < 0.01$

baseline v. late drug,  $t = 2.33$ ,  $df = 9$ ,  $p < 0.05$

baseline v. withdrawal,  $t = 0.12$ ,  $df = 9$ , (n.s.)

early drug v. late drug,  $t = 1.51$ ,  $df = 9$ , (n.s.)



TABLE 3.15. EFFECT OF NITRAZEPAM ON SLEEP

Mean total min of stage REM sleep accumulated in hours 4 to 7 of sleep. Each value for each of 10 subjects is the mean of 6 nights.

Subjects	Mean min of REM sleep in hours 4 to 7 of sleep			
	Baseline pre-drug	Early drug	Late drug	Withdrawal
BB	54.5	71.8	61.4	60.4
MC	66.5	72.2	76.6	67.2
JG	63.1	55.5	65.3	63.1
GH	55.0	51.6	54.8	74.2
GJ	67.6	65.7	73.3	51.8
DJ	60.8	59.4	72.8	58.1
RMCD	40.4	44.6	48.5	45.9
JR	79.7	60.7	72.6	53.3
MS	56.9	54.7	61.5	63.3
MT	48.7	49.1	70.9	33.1
Mean	59.3	58.5	65.8	57.0
± S.D.	± 10.9	± 9.3	± 9.1	± 11.7

#### Statistical analysis

##### (a) Friedman's analysis of variance

$$\chi^2_r = 8.07, df = 3, p < 0.05$$

##### (b) t-tests for paired observations (2-tailed)

baseline v. early drug,  $t = 0.27$ ,  $df = 9$ , (n.s.)

baseline v. late drug,  $t = 2.61$ ,  $df = 9$ ,  $p < 0.05$

baseline v. withdrawal,  $t = 0.54$ ,  $df = 9$ , (n.s.)

early drug v. late drug,  $t = 2.75$ ,  $df = 9$ ,  $p < 0.05$

TABLE 3.16. EFFECT OF NITRAZEPAM ON SLEEP

Lack of influence of nitrazepam 5 mg on the latency from sleep onset to the first appearance of REM sleep. Each value for each of 10 subjects is the mean of 6 nights.

Subjects	REM sleep latency (mean min)			
	Baseline pre-drug	Early drug	Late drug	Withdrawal from drug
BB	70.6	64.5	96.8	60.3
MC	45.9	84.5	69.1	49.8
JG	80.5	87.4	86.7	72.0
GH	107.8	120.0	68.6	82.7
GJ	82.8	78.1	86.1	78.6
DJ	48.4	66.8	56.2	37.5
RMcD	61.7	137.6	118.5	104.8
JR	107.8	109.7	105.1	100.8
MS	90.8	76.3	76.4	63.3
MT	119.7	95.6	104.4	172.4
Mean	81.6	92.0	86.8	82.2
± S.D.	± 25.4	± 23.8	± 19.6	± 38.0

Friedman's analysis of variance

$$\chi^2_r = 5.88, df = 3 \text{ (n.s.)}$$

TABLE 3.17. EFFECT OF NITRAZEPAM ON SLEEP

Mean total min of stages 3 + 4 accumulated in the first 6 h of sleep for each individual subject. Each value for each of 10 subjects is the mean of 6 nights.

Subjects	Mean min of stages 3 + 4			
	Baseline pre-drug	Early drug	Late drug	Withdrawal
BB	94.8	64.0	51.5	88.1
MC	15.4	7.8	4.2	1.8
JG	59.8	51.4	47.7	43.4
GH	51.1	45.3	34.0	56.7
GJ	103.0	100.0	92.4	88.3
DJ	104.4	98.2	78.6	101.7
RMcD	92.7	57.3	18.4	104.2
JR	59.3	22.6	38.7	69.0
MS	78.4	52.9	25.4	77.0
MT	131.1	113.3	108.4	97.1
Mean	79.0	61.3	49.9	72.7
± S.D.	± 33.3	± 34.0	± 33.5	± 31.8

#### Statistical analysis

##### (a) Friedman's analysis of variance

$$\chi^2_r = 14.88, df = 3, p < 0.005$$

##### (b) t-tests for paired observations (2-tailed)

baseline v. early drug,  $t = 4.22$ ,  $df = 9$ ,  $p < 0.01$

baseline v. late drug,  $t = 4.34$ ,  $df = 9$ ,  $p < 0.01$

baseline v. withdrawal,  $t = 1.42$ ,  $df = 9$ , (n.s.)

early drug v. late drug,  $t = 2.40$ ,  $df = 9$ ,  $p < 0.05$



PART (5): GENERAL DISCUSSION OF CHAPTER 3

AN INVESTIGATION INTO THE EFFECTS OF A PLACEBO, HORLICKS  
AND OF NITRAZEPAM ON SLEEP

The original intention behind the design of this experiment had been to compare the long-term effectiveness of the bedtime food drink, Horlicks, with that of nitrazepam in improving sleep, but the failure of Horlicks to influence sleep showed that it obviously does not possess sleep-promoting qualities comparable to an hypnotic drug. This was very apparent in this experiment where nitrazepam was so superior in reducing wakefulness that interrupted sleep and in prolonging the sleep of the same ten subjects, who showed no significant change when Horlicks was taken at bedtime. However, this does not negate the findings of Brezinová and Oswald (1972), for their study included a restriction on eating after 1900h and in retrospect this may well be a crucial point, for although Horlicks may not possess inherent sleep-promoting properties it may well have proved better than nothing at bedtime had subjects been instructed not to eat or drink after about 1900h.

The study did show the effectiveness of nitrazepam as an hypnotic over a relatively long period of use, but it also underlined the disadvantages of drug-induced sleep. From the point of view of the patient taking/

taking the drug, the greatly increased amounts of waking through the night following withdrawal from the drug is an obvious disadvantage. Other negative points include the slowness of elimination of the drug from the body (Rieder and Wendt, 1973). The slowness of elimination must contribute to the hangover effects manifested as impairment in psychomotor performance the following day (Malpas et al., 1970).

The distortion of the normal pattern of REM sleep and the reduction of slow wave sleep during nitrazepam administration raises the question of whether drugged sleep is as good as drug-free sleep. I suppose it depends upon what you think sleep is for. If it is just a behavioural adaptation to the environment, then presumably modifications of the distribution of sleep stages is of little consequence. However, this strikes me as a naive approach to the function of sleep in view of the wealth of evidence linking restorative processes with sleep and so if the normal pattern of REM sleep and slow wave sleep is disturbed by taking nitrazepam, and these are the stages of sleep which have been particularly linked with the recuperative role of sleep, then maybe drugged sleep is inferior. However, I will leave discussion of this question until the end of the following section, for it includes some data pertinent to this question.

In/

In contrast to the changes in sleep found with nitrazepam, was the absence of any measureable effect on sleep when the placebo was compared with no-treatment. Subjects were specifically told that the placebo was a sleeping pill and so this indicates, at least in these subjects, that suggestion alone is not sufficient to alter sleep and that the influence of nitrazepam is due to its pharmacological actions.



# CHAPTER 4

## THE EFFECTS OF BEDTIME EATING AND OF NITRAZEPAM ON THE NOCTURNAL COMPOSITION OF PLASMA

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## CHAPTER 4

### SUMMARY

Seven middle-aged volunteers had their blood sampled overnight before and during chronic administration of Horlicks and of nitrazepam 5mg.

Nitrazepam had no significant effect on the plasma levels of growth hormone, glucose, triglycerides or cholesterol, but Horlicks at bedtime led to a significant elevation of plasma triglycerides.

## INTRODUCTION

The aim of this study was to investigate any changes in the nocturnal plasma levels of growth hormone, glucose, cholesterol and triglycerides when volunteers took either a food drink or nitrazepam at bedtime.

Human growth hormone (GH) is released soon after sleep onset (Takahashi et al., 1968; Honda et al., 1969) and at least in young adults is linked to the appearance of slow wave sleep stages 3+4 (Sassin et al., 1969a). Factors which alter GH secretion during waking hours have much less effect on the sleep related release of GH, for example, induction of acute or chronic hyperglycemia prior to or with the onset of deep sleep has not been found to alter subsequent GH release (Parker and Rossman, 1971; Schnure et al., 1971). The sleep dependent release of GH immediately responds to a shifted sleep schedule. If sleep is delayed for several hours then GH release is withheld until after the new time of onset of sleep (Takahashi et al., 1968) and if subjects are selectively deprived of slow wave sleep then GH secretion is suppressed (Sassin et al., 1969b; Schnure et al., 1971).

GH promotes RNA and protein synthesis and stimulates uptake of amino acids into tissues (Korner, 1965).

In/



In Chapter 1 of this thesis, evidence was presented in favour of the view that the major function of sleep is for restoration and repair of both the body and the brain and that the sleep-dependent secretion of growth hormone is complementary to the already favourable conditions for anabolic processes. Many hypnotic drugs, particularly the benzodiazepines, reduce the amount of time spent in slow wave sleep. In the previous chapter (part 4) nitrazepam was reported progressively to reduce the min of SWS over a number of weeks of administration and this has been found for other benzodiazepines by various investigators, referred to in that section. So the question arises, is there a concomitant diminution in the amount of GH secreted during sleep? What evidence there is, suggests that during drug administration GH secretion is not reduced. Ogunremi et al. (1973) reported that chronic ingestion of either sodium amylobarbitone or the tranquillizer benzocetamine did not effect the nocturnal GH levels of their eight young men volunteers although SWS was reduced by amylobarbitone. Withdrawal from either drug resulted in an elevation in the GH peak which returned to baseline levels by the third week after withdrawal. It was not stated if this elevation of the GH peaks was significant but if they were then it does/

does suggest that during use, some process related to GH production, secretion, action, and/or inactivation has been affected. Rubin et al. (1973b) similarly reported that the release pattern of GH was not altered by administration of flurazepam 30mg for three weeks to one subject. GH secretion was not consistently altered by the administration of the benzodiazepines, diazepam (Stokes et al., 1972) or flurazepam (Bixler et al., 1976). In the latter study two young male insomniacs were studied before, during and after drug administration. Drug administration in both studies was associated with reduction in slow wave sleep.

Nitrazepam is also a benzodiazepine and so was predicted not to influence GH secretion. No predictions were made about the other blood constituents.

I said earlier that the sleep-dependent GH secretion is remarkably resistant to hyperglycemia and no correlation has been found between plasma glucose, cortisol or insulin concentrations and GH release during sleep (Takahashi et al., 1968), however, elevation of plasma free fatty acids (FFA), by oral administration of corn oil and iv heparin, resulted in a considerable depression of growth hormone release during sleep (Lipman et al., 1972). GH is a lipolytic hormone and so elevates FFA. The reduction of GH secretion associated/

associated with an elevation of FFA suggests that a negative feedback operates between GH secretion and plasma FFA, and raises the possibility that evening nutrition could influence the nocturnal secretion of GH. The bedtime food drink Horlicks is made from triple concentrated full cream milk, sucrose, malted barley and wheat flour and was predicted to raise the plasma glucose and triglyceride levels. No predictions were made as regards the plasma cholesterol levels.



## METHODS

### (a) Subjects and experimental design

Seven volunteers, four men and three women, took part in this study. Their average age was 59y (ranging from 53y to 63y). They had taken no drugs in the preceding months and during the entire experimental period they were asked to consume no alcohol and take no drugs other than those given by us. In this experiment, there was no restriction on the time for eating their evening meal, or taking a snack prior to attending the sleep laboratory.

Subjects attended the laboratory in pairs to sleep in quiet and comfortable bedrooms.

On all nights subjects had one channel of parieto-occipital electroencephalogram, two channels of bipolar eye movements and one channel of submental muscle tone recorded. On treatment nights one of the pair received nitrazepam 5mg and the other Horlicks (32g Horlicks powder mixed with 250ml hot milk) half an hour before the evening recording began. This investigation was an adjunct to the experiment which was designed to compare sleep after the food drink Horlicks with sleep after the benzodiazepine, nitrazepam (described in Chapter 3). The combined experimental design is shown below to illustrate that the apparently isolated blood night/

night during week 6, did in fact occur after several nights of sleep at the laboratory.

Experimental design:

Weeks 1 and 2	2 Adaptation nights, 6 baseline nights, 1 Adaptation blood night, 1 BASELINE BLOOD NIGHT
Weeks 5 and 6	1 Adaptation night, 6 early treatment nights, 1 EARLY TREATMENT BLOOD NIGHT
Weeks 11 and 12	1 Adaptation night, 6 late treatment nights, 1 Adaptation blood night, 1 LATE TREATMENT BLOOD NIGHT
Weeks 15 and 16	1 Adaptation night, 6 withdrawal nights

Each treatment was taken from the first recorded night during week 5 and every night up to and including the night preceding the first withdrawal night during week 15.

After six weeks on no treatment the entire 16 week schedule above was repeated, for the other treatment. Subjects took their treatments in balanced order.

(b) Nocturnal sampling of blood

The study of nocturnal constituents of plasma involved the ten blood nights in the schedule above (four adaptation and six measurement blood nights). The results presented are from the six measurement BLOOD NIGHTS. On all nights, subjects had a catheter inserted into a forearm vein. The catheter had an extension/

extension of fine plastic tubing of sufficient length (approx. 8 ft) to pass through the bedroom wall and allow the subject freedom of movement. The catheter plus extension had a deadspace volume of about 6ml, which was filled with heparinized saline (10,000 IU/1) to prevent clotting. On the six measurement nights, blood was sampled every 30 min. First the dead space volume of heparinized saline plus 1ml of blood was drawn into a 10ml syringe attached to the experimenter-end of the extension tube. The syringe was discarded, a new syringe attached and a 10ml blood sample taken. As the blood sample was taken a mark was made by a marker pen on the EEG machine on the sleep recording to pin-point the time that the sample was taken. After each blood sampling the catheter and extension deadspace were quickly refilled with heparinized saline. The 10ml blood sample was centrifuged for 4 min at 1200g to separate the plasma, aliquots were taken and then stored deep-frozen ( $-20^{\circ}\text{C}$ ) in labelled tubes until assayed.

#### (c) Analysis of sleep recordings

The electrophysiological recordings of sleep made on the measurement blood nights were read 'blind' as to the experimental condition and categorized into the various sleep stages according to the criteria of Rechtschaffen/



Rechtschaffen and Kales (1968). As the recordings were read a note was made of each of the page numbers where there was a marker to show a blood sample had been taken. A computer programme calculated the number of minutes spent in each of the sleep stages, 1, 2, 3, 4 and REM and wakefulness in the accumulation of each successive hour of sleep.

(d) Analysis of blood constituents

(i) Plasma growth hormone (GH)

The GH concentration in each sample was assayed 'blind' as to the experimental condition by the Edinburgh MRC Radioimmunoassay Team using the method of Hunter (1972).

The GH results were expressed as the concentration in mU/l (in terms of human GH international reference preparation 66/217) at the clock time when the blood sample was taken. However, the page numbers where the EEG paper was labelled by the marker pen were used in the calculations.

In conjunction with the recordings of sleep, the page number when a blood sample was taken was converted into min after the first onset of sleep. This was done by subtracting the number of the page, on the overnight recording, when the subject first fell asleep from the page number of the first blood sample. The difference was/

was then divided by the paper speed (calculated by computer), to give the time that elapsed from sleep onset in min. The same procedure was used to convert all the page numbers when a blood sample had been taken into min after sleep onset.

Graphs were plotted, for each subject, of the GH concentration at the time in min after the first onset of sleep. Wakefulness occurring after the first onset of sleep was included in the calculations. Some of the GH concentrations were below the sensitivity threshold of the assay system and were reported as a concentration of  $<1\text{mU/l}$ . These results were plotted on the graphs as equal to  $0.5\text{mU/l}$ .

The area under the GH curves from sleep onset to six hours later, was measured by a planimeter in  $\text{cm}^2$  for each individual night. The vertical scale was  $1\text{cm}/1\text{mU/l}$  of GH and the horizontal scale was  $2\text{cm}/\text{hour}$ .

To average the GH results from all seven subjects, the times when the blood samples were taken were converted into minutes after sleep onset. This was done for each subject on every blood night and then the results were averaged for any one experimental condition by collating all the samples taken during the first 30 min, during 30.1 to 60 min after sleep onset and so on in blocks of 29.9 min up to 390.1 to 420 min after sleep onset. If any subject had had two blood samples taken within one period, the average was used in the calculation of the group mean.

(ii) Plasma glucose concentrations

The plasma glucose (as well as plasma cholesterol and triglycerides) were estimated by the Department of Clinical Chemistry of the Edinburgh Royal Infirmary.

Plasma samples for estimation of the glucose concentration were collected on some but not all nights for each subject. The samples were later assayed, by the method of Morley et al. (1968) and the concentration expressed in mg glucose/100ml plasma at the clock time that the blood sample was taken.

(iii) Plasma cholesterol and triglyceride concentrations

The cholesterol concentration (mg/100ml plasma) was measured in each sample and the results were presented as the concentration at the clock time when the sample was taken.

The cholesterol concentration was assayed by the automated colorimetric method of Levine and Zak (1964). The triglyceride concentration was estimated in each plasma sample by the method of Kessler and Lederer (1965). The results were reported in terms of the triglyceride concentration (mg/100ml plasma) at the time on the clock when the blood was sampled.

To/



To obtain means of the results from all seven subjects for the plasma cholesterol and triglyceride levels each blood night was divided into 30 min periods, i.e. 2300h to 2330h; 2330h to 2400h and so on through the night. The results from each subject, for each constituent, were allocated to their appropriate 30 min periods according to the clock time when the blood sample had been taken. Thus, for example, all the plasma triglyceride results for the early Horlicks blood night were collected together into their appropriate 30 min periods through the night. Thereafter the mean of each 30 min period was calculated.

The data for all the tables of means for the thirds of the night (2300h to 0130h, 0130h to 0400h and 0400h to 0630h) were calculated by averaging all the values of the particular blood constituent for each subject sampled within the specified hours.

The data for the graphs of the mean levels were achieved by dividing the night into a series of 30 min periods as described above. An attempt was made to sample blood every 30 min but occasionally it was impossible to obtain a sample and so some of the 30 min periods lack a value from one or more subjects and the mean for that period was attained by dividing by a number smaller than seven.

(e)/

(e) Statistical analysis

t-tests for paired observations (Ferguson, 1959) were used to compare the results of each of the treatments with the baseline values.

## RESULTS

### (a) Nocturnal growth hormone concentration

Figure 4.1 shows the mean GH concentrations plotted for the baseline period and during early and late Horlicks administration. The mean concentrations are plotted at the midpoints of the spans of time after sleep onset over which the means were calculated i.e. the mean of the GH values falling in the block of time 0 to 30 min after the first onset of sleep is plotted on the graph at 15 min after the first onset of sleep. Figure 4.2 similarly shows the mean baseline results and those, during early and late nitrazepam administration.

Table 4.1 shows the areas under these curves between the onset of sleep and 360 min after first falling asleep. Individual areas are presented to illustrate the influence on the mean values of one subject (MT) in particular, who contributed disproportionately to the relatively higher GH values on the mean late drug blood night. The areas under the individual subjects' GH curves were used for statistical comparison of the nocturnal GH responses under the different conditions.

There were no significant differences between either of the treatments and their corresponding baseline period when the results from the first 6h of sleep were compared.



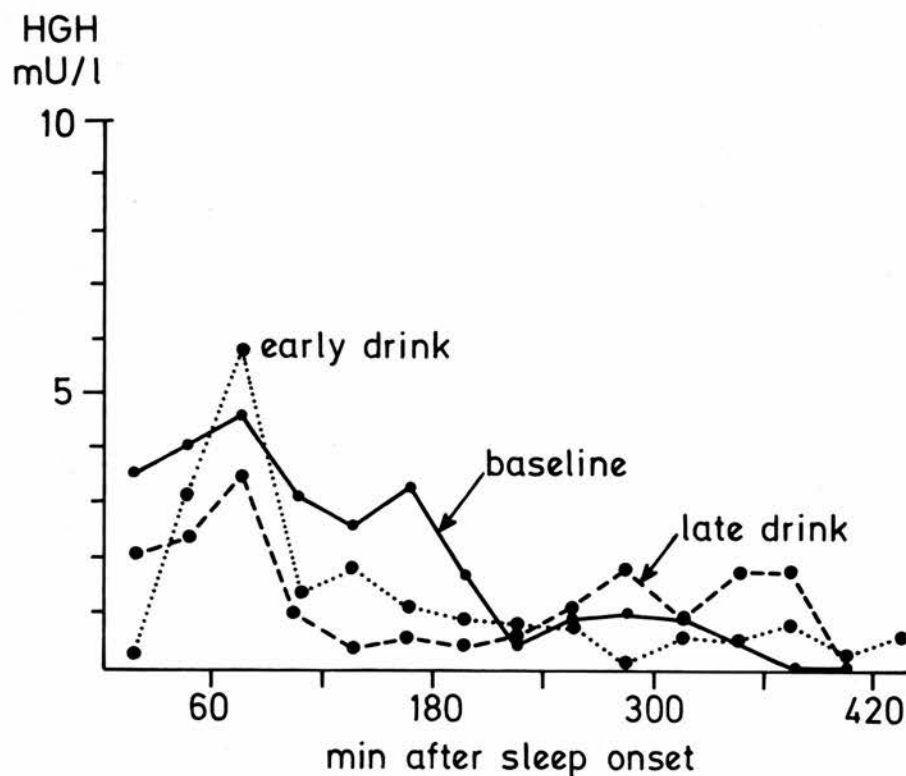


FIGURE 4.1 Mean nocturnal plasma growth hormone concentrations before, near the beginning and near the end of a 10 week period of taking a milk and cereal food drink (Horlicks) every night.

Each value is the mean of 7 subjects.

Note: The graphs above have been photographically reduced ( $\times 0.72$ ). The areas under each of the curves is presented in Table 4.1 and refer to the areas before photographic reduction.

For clarity the S.D. of each point on the graph has been omitted but Table 4.1 gives an indication of inter-individual variance.

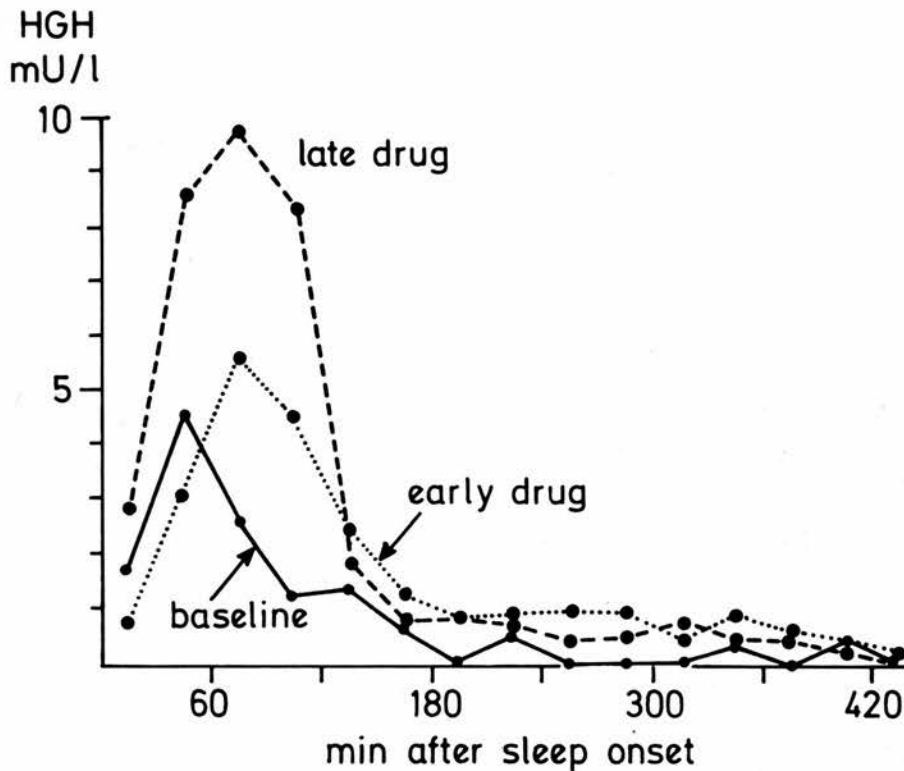


FIGURE 4.2 Mean nocturnal plasma growth hormone concentrations before, near the beginning and near the end of a 10 week period of taking nitrazepam 5mg every night.

Each value is the mean of 7 subjects.

Note: The graphs above have been photographically reduced ( $\times 0.72$ ). The areas under each of the curves is presented in Table 4.1 and refer to the areas before photographic reduction.

For clarity the S.D. of each point on the graph has been omitted but Table 4.1 gives an indication of inter-individual variance.

However, there does appear to be a trend of higher values during nitrazepam administration. Six out of seven subjects in the early drug period and five out of seven during the late drug period had higher values than baseline for their GH response graphs, integrated from sleep onset to 360 min after the first onset of sleep. Conversely there is an indication of lower GH levels during Horlicks administration, with six out of seven subjects having lower GH responses in the early food drink period and five out of seven in the late drink period than on the baseline blood night. However, the variance was high on all these means and none of the differences were significant. Table 4.2 shows the mean integrated GH responses subdivided into the first 3h and second 3h after sleep onset. No significant differences were found during the first 3h after sleep onset for either Horlicks or nitrazepam, when compared with their respective baseline periods. Statistical comparison, by t-tests for paired observations, of the GH responses, under the different conditions, integrated from 180 to 360 min after sleep onset showed that the GH responses during the early drug period were significantly greater than those found during the preceding baseline period. As this was the only significant finding in all the integrated GH results, and it is only at the 1 in 20 level of significance, not too much weight should be given to it.



(b) Nocturnal plasma glucose concentration

Samples for blood glucose estimation were not taken under all conditions for all subjects, therefore group means on the raw data are inappropriate. Figures 4.3; 4.4; 4.5 illustrate the graphed results of the three subjects who had had their blood sampled for glucose estimation before and during Horlicks administration. Figures 4.6; 4.7 show the individual results for the two subjects who had their blood sampled before and during nitrazepam 5mg administration. No consistent pattern of change in nocturnal blood glucose level can be seen either after taking Horlicks before retiring to bed or during nitrazepam administration.

(c) Nocturnal plasma cholesterol concentration

Figure 4.8 shows the mean concentration of plasma cholesterol at 30 min intervals through the night. The group means are plotted at the midpoint of each 30 min span. There appears to be a slight elevation throughout the night of plasma cholesterol when Horlicks had been taken 30 min before bed, but no consistent changes during nitrazepam administration. Table 4.3 shows the lack of effect of both Horlicks and nitrazepam administration on levels of plasma cholesterol through the night.

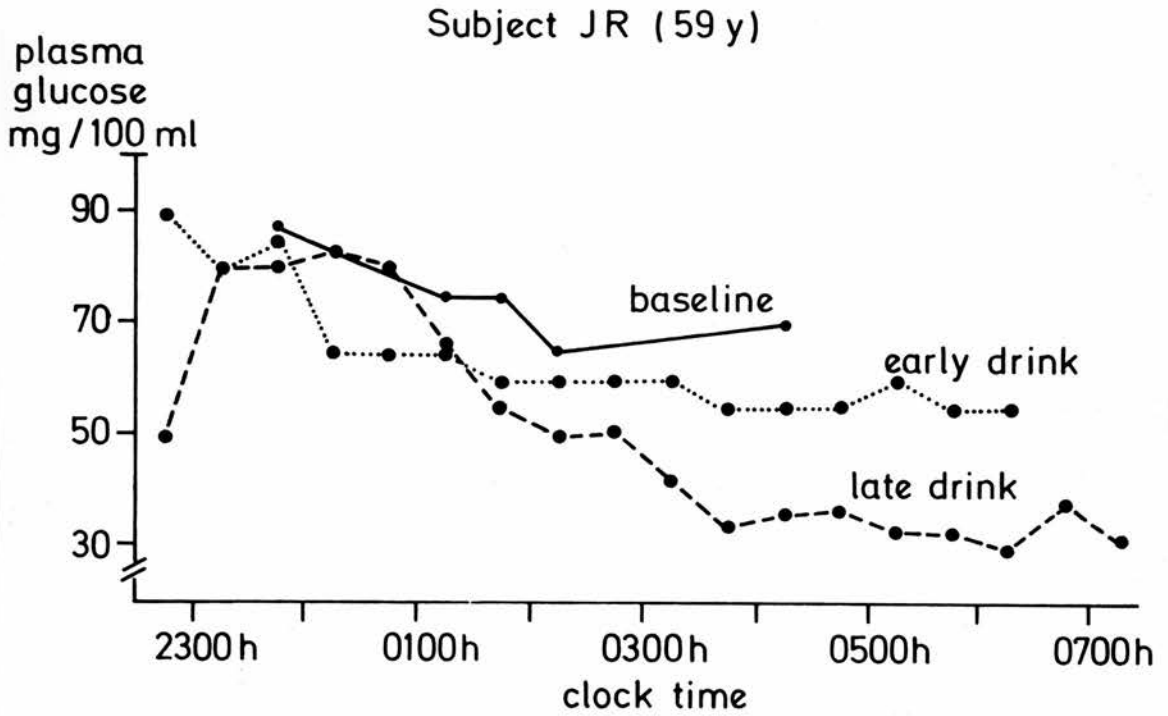


FIGURE 4.3 Nocturnal plasma glucose concentrations of the female subject JR before, near the beginning and near the end of a 10 week period of taking a milk and cereal food drink (Horlicks) every night.

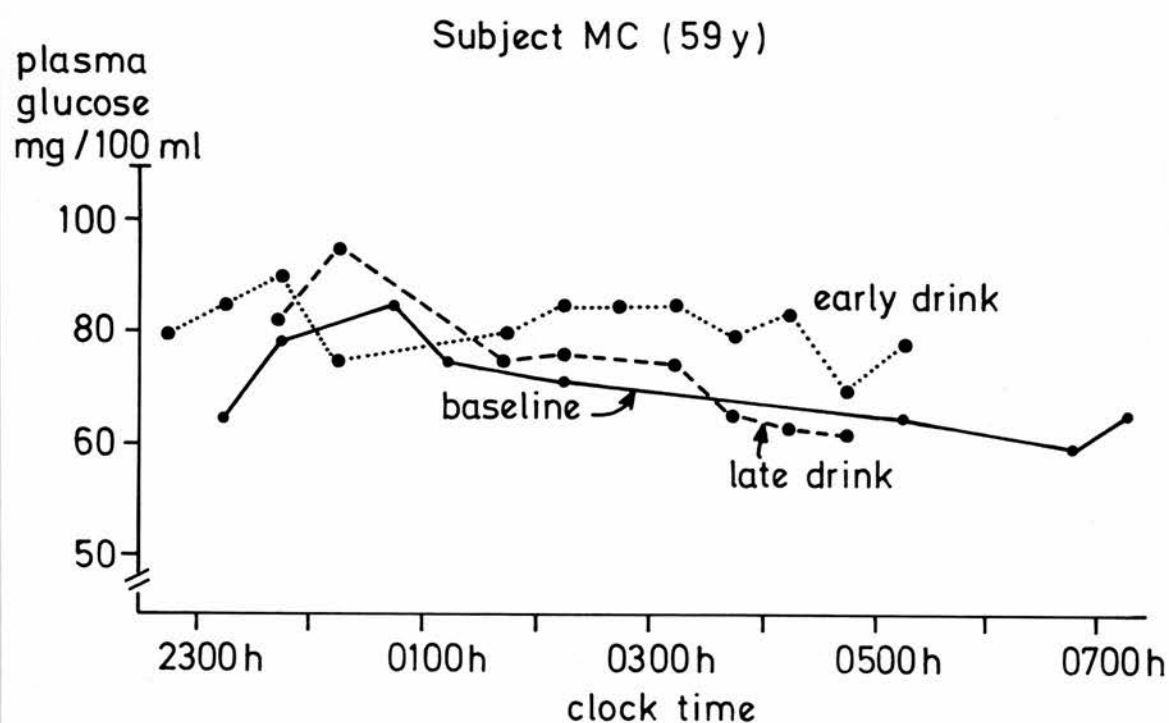


FIGURE 4.4 Nocturnal plasma glucose concentrations of the male subject MC, before, near the beginning and near the end of a 10 week period of taking a milk and cereal food drink (Horlicks) every night.



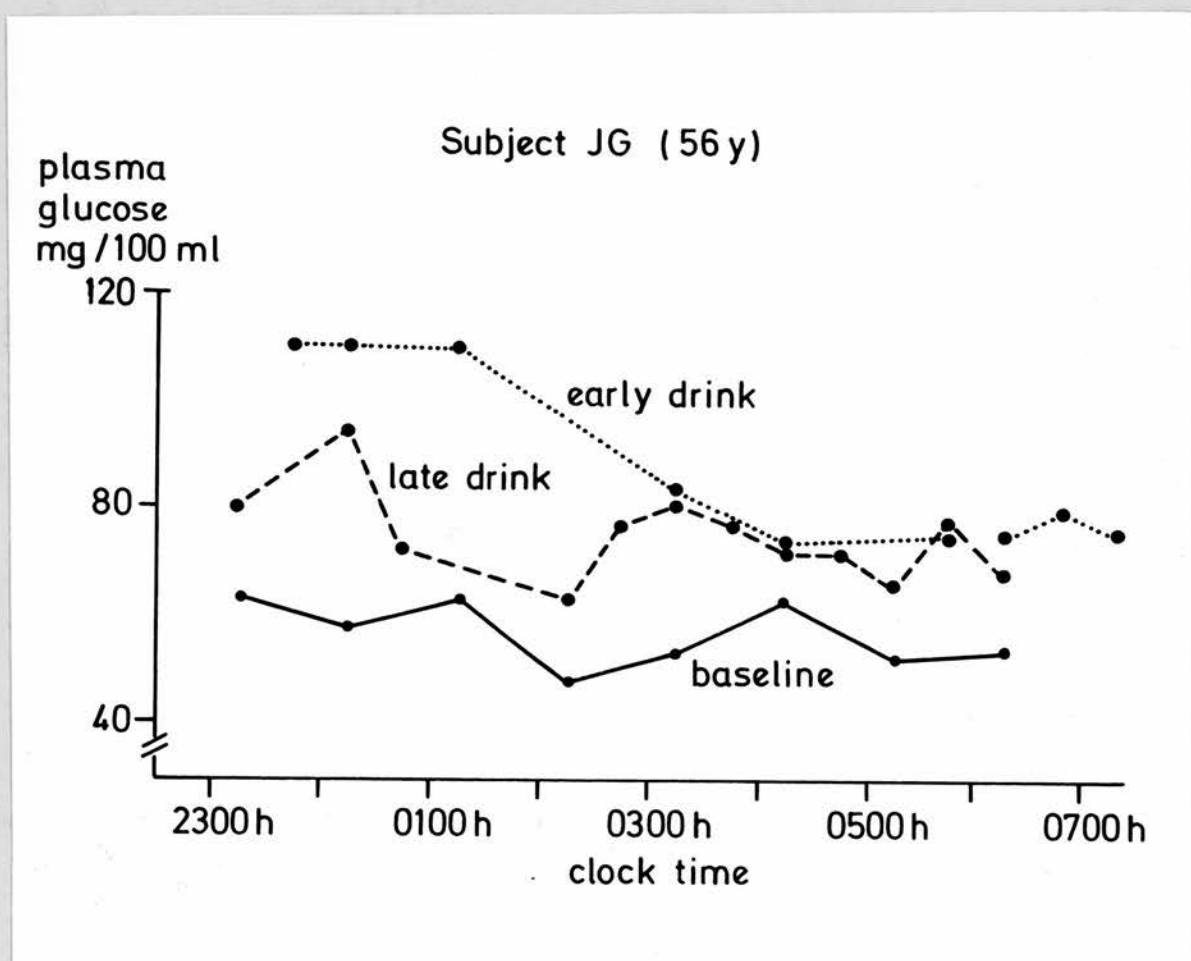


FIGURE 4.5 Nocturnal plasma glucose concentrations of the male subject JG before, near the beginning and near the end of a 10 week period of taking a milk and cereal food drink (Horlicks) every night.

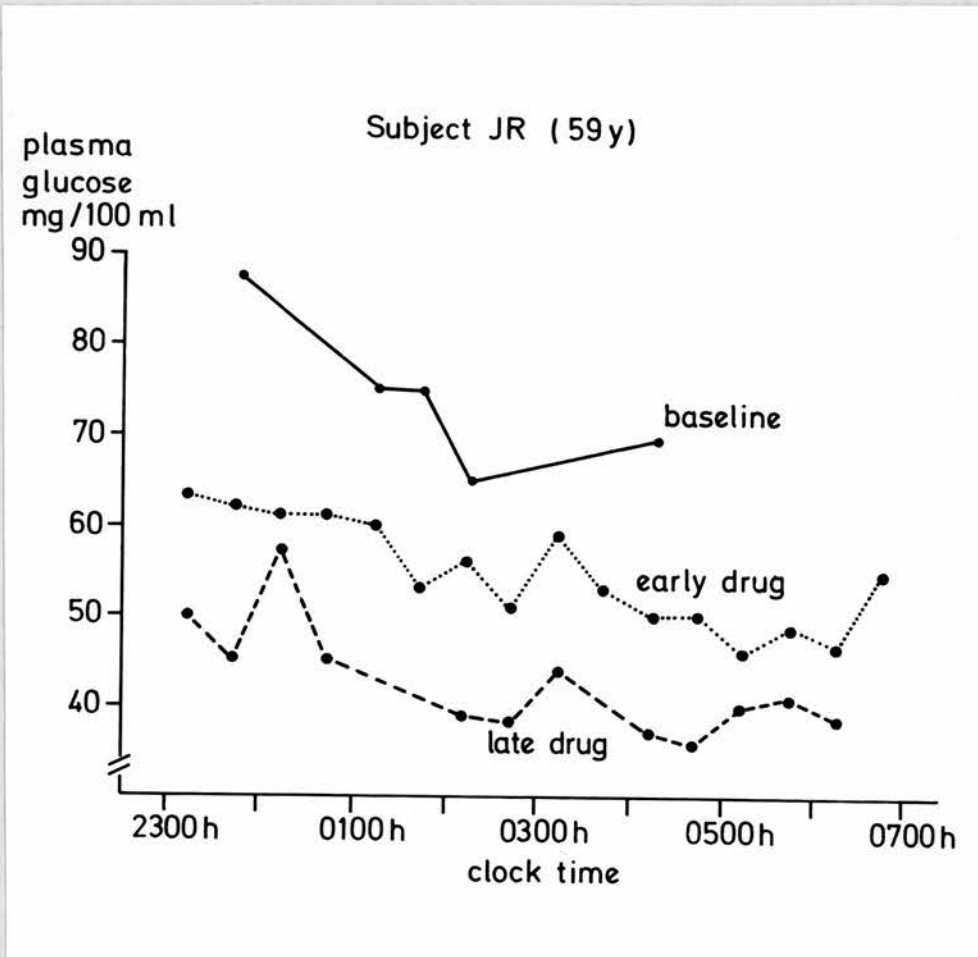


FIGURE 4.6 Nocturnal plasma glucose concentrations of the female subject JR before, near the beginning and near the end of a 10 week period of taking nitrazepam 5mg every night.

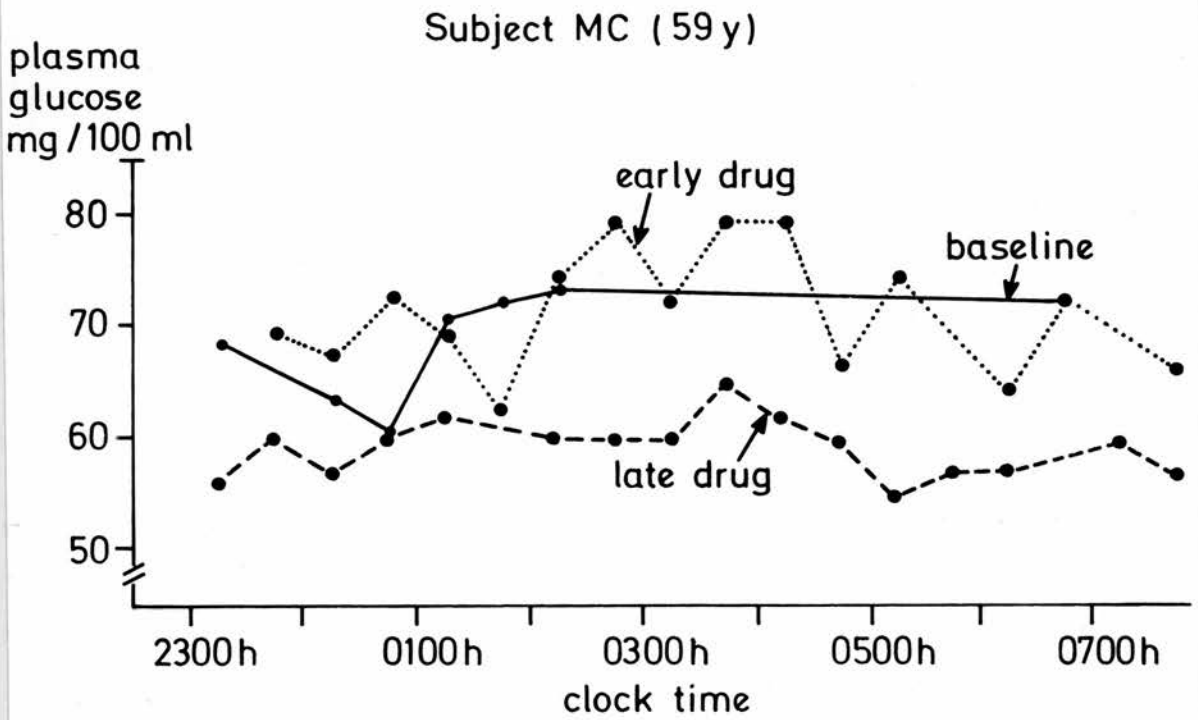
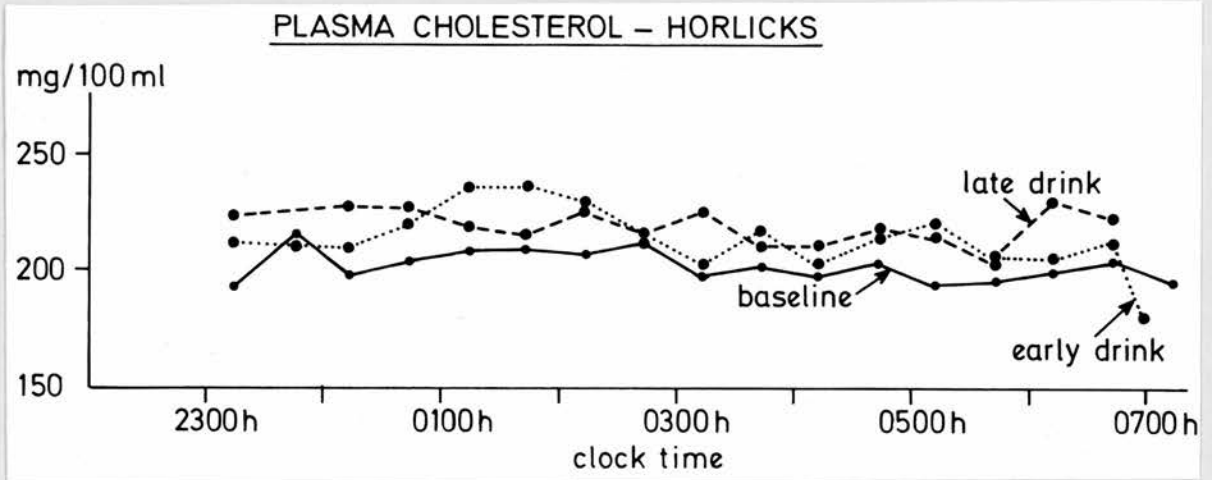


FIGURE 4.7 Nocturnal plasma glucose concentrations of the male subject MC before, near the beginning and near the end of a 10 week period of taking nitrazepam 5mg every night.



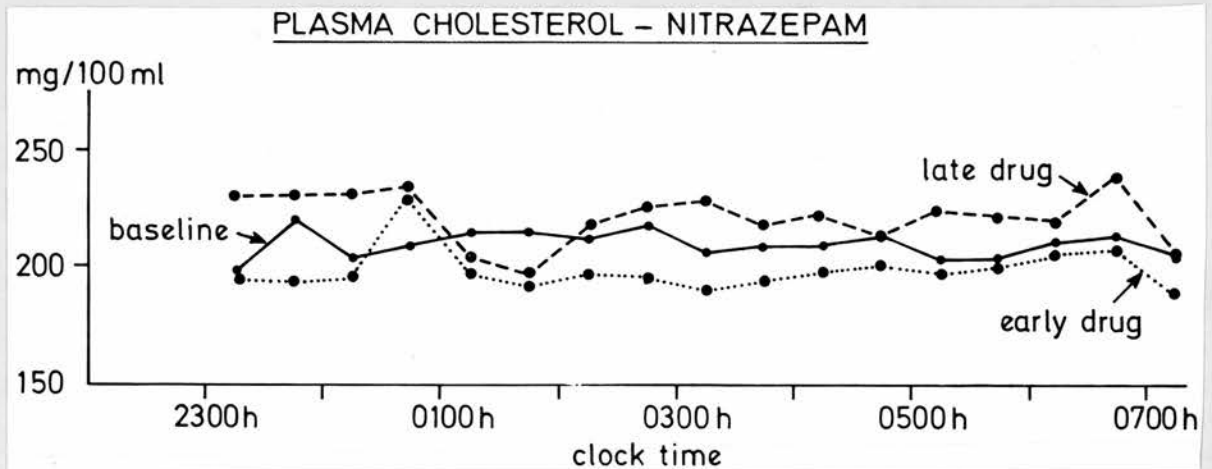
FIGURE 4.8



(a) Mean nocturnal plasma cholesterol concentrations before, near the beginning and near the end of a 10 week period of taking a milk and cereal food drink (Horlicks) every night.

Each point on the graph is the mean of 7 subjects.

Note: For the sake of clarity the S.D. of each mean value has been omitted. Table 4.3 gives an indication of inter-individual variance.



(b) Mean nocturnal plasma cholesterol concentrations before, near the beginning and near the end of a 10 week period of taking nitrazepam 5mg every night.

Each point on the graph is the mean of 7 subjects.

Note: Table 4.3 gives an indication of inter-individual variance.

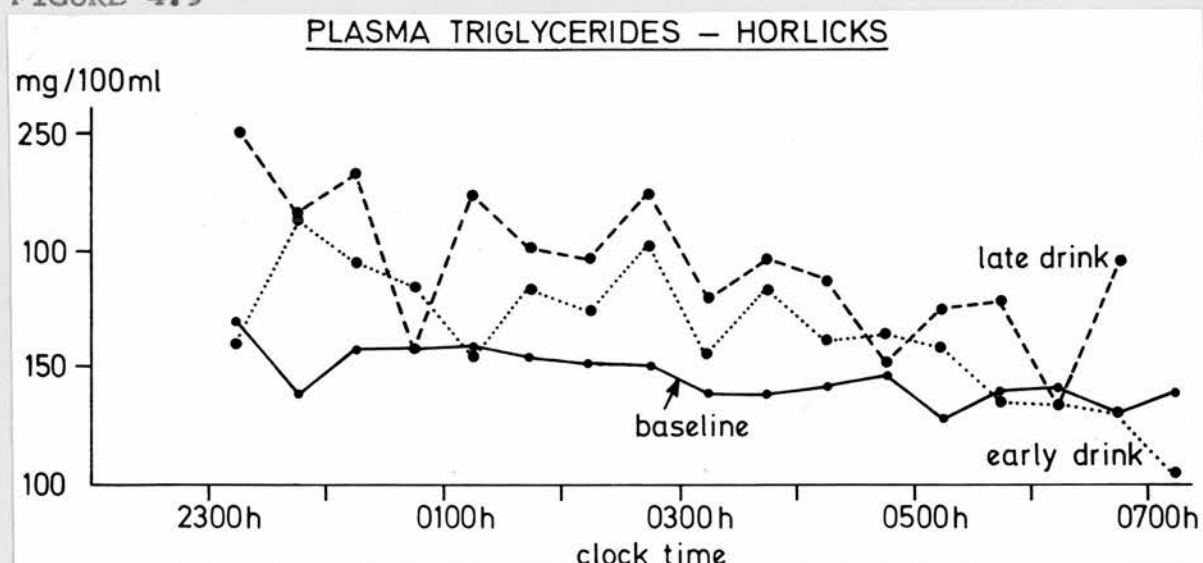
(d) Nocturnal plasma triglyceride concentration

Figure 4.9 illustrates the elevation of plasma triglycerides found after Horlicks had been taken 30 min before bedtime. There was no such rise after nitrazepam 5mg. Table 4.4 shows the mean triglyceride levels during the first, second and last thirds of the night. t-tests for paired observations revealed that the plasma triglyceride levels were significantly elevated during the late Horlicks period, whether the means for the whole night (2300 - 0600h), the first two-thirds of the night (2300h - 0400h) or the first third (2300h - 0130h) were considered. Table 4.5 lists individual subjects mean triglyceride levels subdivided into three sections of the night before, at the beginning and after prolonged nightly Horlicks administration.

(e) Lack of correlation between amount of time spent in SWS and growth hormone output.

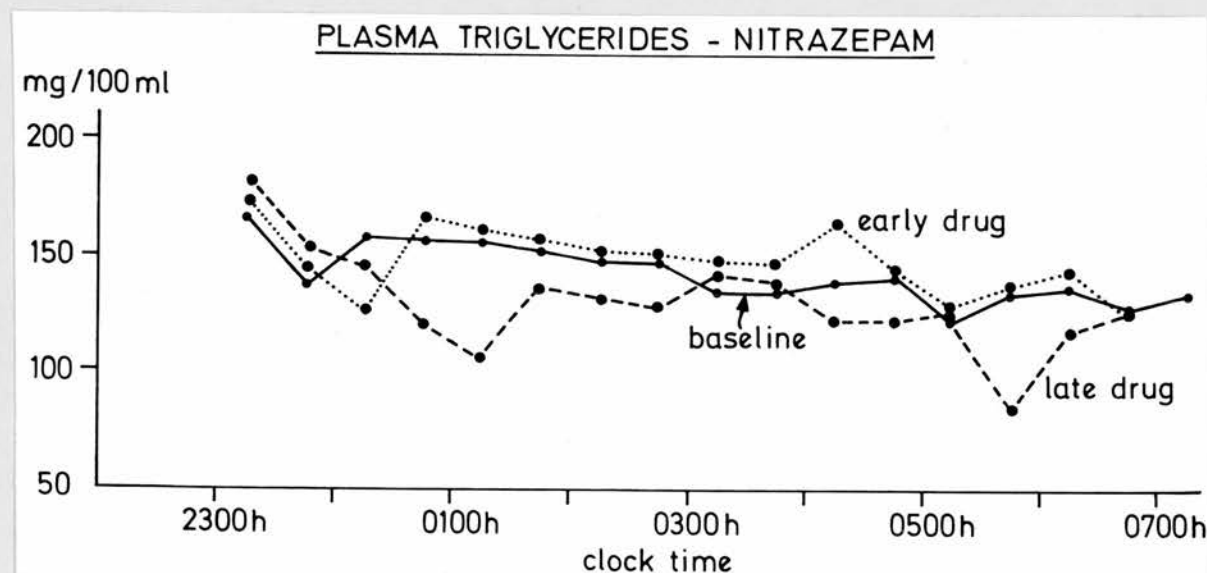
Table 4.6 shows the mean min of slow wave sleep (SWS) accumulated by each subject in the first 6h of sleep on the blood night recorded during the pre-drug baseline period and the blood night recorded during the pre-food drink period paired with the integrated growth hormone response data (From Table 4.1). The mean min of SWS were not significantly correlated with the integrated growth hormone data on either the pre-drug:  $r = -0.42$ ,  $df = 5$  (n.s.) or the pre-food drink:  $r = 0.35$ ,  $df = 5$  (n.s.) blood night.

FIGURE 4.9



(a) Mean nocturnal plasma triglyceride concentrations before, near the beginning and near the end of a 10 week period of taking a milk and cereal food drink (Horlicks) every night.

Each point on the graph is the mean of 7 subjects.  
Note: For the sake of clarity the S.D. of each mean value has been omitted. Table 4.5 gives an indication of both intra and inter-individual variance.



(b) Mean nocturnal plasma triglyceride concentrations before, near the beginning and near the end of a 10 week period of taking nitrazepam 5mg every night. Each point on the graph is the mean of 7 subjects.

Note: Table 4.4 gives an indication of the inter-individual variance.



NOTE: The data for all the tables of means for the thirds of the night were calculated by averaging all the values of levels of the particular constituent for each subject within the hours specified. The data for the graphs of the mean levels were achieved by dividing the night into a series of 30 min periods. We tried to sample blood every 30 min but occasionally it was impossible to obtain a sample and so some of the 30 min periods lacked a value from one or more subjects and the mean for that period was attained by dividing by a number smaller than seven. This difference in the method of calculation is the reason why there is a discrepancy among the group means illustrated in the graphs and the average of the individual subjects' means shown in the tables.

## DISCUSSION

The design of this study allowed at least eight weeks on both Horlicks and nitrazepam by the time of the late treatment blood night and so any effects due to chronic use were expected to appear by then. Unfortunately, there was no blood night during withdrawal from either treatment. It would have been interesting to see if the suggestion of an upward trend in GH secretion during chronic nitrazepam use was followed by a decrease or increase in GH response on withdrawal of the drug. The trend of increased GH during drug use was not significant and so any speculations may be spurious but it is tempting to think that an adaptive increase in GH secretion had occurred during drug administration to offset some detrimental effect of the drug and that on withdrawal this adaptation would still be present and could thus lead to a further increase in nocturnal GH release when the drug was no longer present in the body.

In Chapter 3, it was reported that chronic administration of nitrazepam 5mg led to a progressive reduction in the total min of slow wave sleep (SWS), however the present study showed that there was not a parallel diminution in the nocturnal secretion of growth/

growth hormone. This finding is consistent with the reports by other investigators, which I cited in the Introduction to the present section. The apparent independence of the amount of growth hormone secretion from the amount of slow wave sleep under conditions of drug administration, has been commented on before (Rubin et al., 1974; Bixler et al., 1976) and suggests that the relationship between the two is 'permissive' and that there is not an obligatory rate of growth hormone secretion associated with x min of SWS.

The lack of correlation between integrated plasma GH levels and the total min of slow wave sleep (SWS) has also been reported by Rubin et al. (1973b) and Schnure et al. (1971) and suggests that although the two may be associated it must be a rather flexible relationship.

It has been proposed by Carlson et al. (1972) and Finkelstein et al. (1972) that there is an age-related diminution in the GH peak during sleep. Carlson et al. found that four out of six of their subjects over 50 years old had no GH peak. All seven subjects in our study were over 50y, but only one of them consistently failed to show a GH peak during sleep. This particular subject was overweight and his body weight was 20% above the ideal for his height and frame/



frame size. Obese patients have been found to lack the sleep-dependent GH peak (Kalucy et al., 1976) and obesity may have accounted for the lack of GH peak in some of the older subjects in the studies above. The reduction in the GH peak after artificial elevation of FFA (Lipman et al., 1972) may provide a clue to the lack of GH peak in obese subjects for studies on fat metabolism suggest that after a short fast (overnight) an obese person tends to have a higher plasma concentration of FFA than normal controls (Bjorntorp et al., 1969).

Blood glucose levels were not consistently changed by either Horlicks or nitrazepam. The absence of effect of Horlicks may be due to the lack of dietary restriction in the later evening. Some of the subjects were taking a snack shortly before coming to the sleep laboratory, on the nights that they knew they were not to be given the food drink, and this might explain the lack of influence of Horlicks on plasma glucose levels.

Horlicks has a fairly high fat content, especially when made up in milk (approximately 20% fat) and this probably accounts for the significant elevation of plasma triglycerides after prolonged intake of the food drink. It is interesting that there was no associated rise in plasma cholesterol, as a high intake of/

of triglycerides is frequently blamed for elevations in cholesterol levels. However with only seven subjects one cannot make bold statements about causes and effects.

High levels of plasma triglycerides have been implicated in ischaemic heart disease (DHSS Report, 1974) and so the elevation of TG during Horlicks use might be a contraindication for people at risk.

To conclude no significant effects of chronic nitrazepam administration were found for nocturnal plasma levels of triglycerides, cholesterol or blood glucose. There were no significant differences among the integrated growth hormone response curves but there was a suggestion of increased growth hormone (GH) secretion during drug administration, which might mean there was a compensatory adaptation in the control of GH levels.

Chronic use of Horlicks had no significant effects on plasma GH, glucose or cholesterol, but there was a significant elevation in triglycerides through the night, which suggests that Horlicks at bedtime should be avoided by patients liable to arteriosclerotic vascular disease.

TABLE 4.1. THE EFFECTS OF BEDTIME EATING AND OF NITRAZEPAM  
ON THE NOCTURNAL COMPOSITION OF PLASMA.

The integrated growth hormone response (GHR).

Each value for each of seven subjects is the area (cm<sup>2</sup>) under the GHR curve from sleep onset to 360 min after sleep onset on one blood night.

$$1 \text{ cm}^2 = 30 \text{ mU}/\beta\text{-min}$$

Areas (cm<sup>2</sup>) under GHR curves

Subjects	HORLICKS			NITRAZEPAM		
	Baseline pre-drink	Early drink	Late drink	Baseline pre-drug	Early drug	Late drug
MC	30.8	64.8	42.0	30.8	47.0	65.8
JG	7.0	6.4	6.0	7.4	9.8	12.8
GJ	37.6	14.0	8.6	21.0	14.0	24.8
DJ	22.2	9.4	31.0	16.2	17.6	6.0
RMCD	38.2	17.0	16.8	25.4	30.4	20.8
JR	29.6	12.8	19.6	22.6	36.6	47.6
MT	32.8	19.6	18.4	7.6	16.6	77.8
Mean	28.3	20.6	20.3	18.7	24.6	36.5
$\pm$ S.D.	$\pm 10.8$	$\pm 20.0$	$\pm 12.5$	$\pm 8.8$	$\pm 13.7$	$\pm 27.6$

t - tests for paired observations: df = 6 (2-tailed).

a) HORLICKS

baseline v early drink: t = 1.03 (n.s.)

baseline v late drink : t = 1.40 (n.s.)

b) NITRAZEPAM

baseline v early drug : t = 1.95 (n.s.)

baseline v late drug : t = 1.68 (n.s.)



TABLE 4.2. THE EFFECTS OF BEDTIME EATING AND OF NITRAZEPAM ON THE NOCTURNAL COMPOSITION OF PLASMA.

The integrated growth hormone response (GHR) sub-divided into the first 3h and the second 3h after sleep onset.

(a) First 3h after sleep onset.

Each value is the mean area ( $\text{cm}^2$ ) under the GHR curve from sleep onset to 180 min after sleep onset. The mean calculated using data from 7 subjects.

HORLICKS		NITRAZEPAM	
Mean area $\pm$ S.D.		Mean area $\pm$ S.D.	
baseline:	21.1 $\pm$ 10.5	baseline:	14.7 $\pm$ 8.3
early drink:	14.8 $\pm$ 21.0	early drug:	17.6 $\pm$ 13.3
late drink:	12.8 $\pm$ 11.3	late drug:	30.8 $\pm$ 27.9
t - tests paired observations: df = 6 (2-tailed).			
baseline v early drink: t = 0.82(n.s.)		baseline v early drug: t = 0.95(n.s.)	
baseline v late drink: t = 1.78(n.s.)		baseline v late drug : t = 1.50(n.s.)	

(b) Second 3h after sleep onset.

Mean areas ( $\text{cm}^2$ ) under GHR curves from 180 min after sleep onset to 360 min after sleep onset

HORLICKS		NITRAZEPAM	
Mean area $\pm$ S.D.		Mean area $\pm$ S.D.	
baseline:	7.2 $\pm$ 5.1	baseline:	4.0 $\pm$ 1.7
early drink:	5.8 $\pm$ 3.9	early drug:	7.0 $\pm$ 3.8
late drink:	7.6 $\pm$ 4.9	late drug:	5.7 $\pm$ 4.4
t - tests for paired observations: df = 6 (2-tailed).			
baseline v early drink: t = 0.72(n.s.)		baseline v early drug: t = 2.83 p<0.05	
baseline v late drink: t = 0.17(n.s.)		baseline v late drug: t = 1.55(n.s.)	

TABLE 4.3. THE EFFECTS OF BEDTIME EATING AND OF NITRAZEPAM ON THE  
NOCTURNAL COMPOSITION OF PLASMA.

Plasma cholesterol levels before and during both Horlicks and nitrazepam administration.

Each value is the mean  $\pm$  S.D. of 7 subjects for the plasma cholesterol level (mg/100 ml plasma) over the particular 2½h sector of the night.

	Mean cholesterol level (mg/100 ml)		
	2300 - 0130h	0130 - 0400h	0400 - 0630h
Mean baseline	217.1 $\pm$ 35.5	212.4 $\pm$ 34.4	210.68 $\pm$ 39.9
early drink	210.9 $\pm$ 49.0	211.2 $\pm$ 50.8	211.2 $\pm$ 49.7
late drink	218.6 $\pm$ 57.4	214.8 $\pm$ 60.4	209.5 $\pm$ 58.2
early drug	206.6 $\pm$ 39.4	189.5 $\pm$ 17.7	195.6 $\pm$ 24.2
late drug	225.5 $\pm$ 57.5	213.6 $\pm$ 56.2	211.5 $\pm$ 51.0

No significant differences were found between baseline values and either treatment.



TABLE 4.4. THE EFFECTS OF BEDTIME EATING AND OF NITRAZEPAM ON THE NOCTURNAL COMPOSITION OF PLASMA.

Plasma triglyceride levels before and during both Horlicks and nitrazepam administration.

Each value is the mean  $\pm$  S.D. of 7 subjects for the plasma triglyceride (TG) level (mg/100 ml plasma) over the particular 2½h sector of the night.

	Mean TG level (mg/100 ml) in the three sectors of the night		
	2300 - 0130h	0130 - 0400h	0400 - 0630h
Mean baseline	167.9 $\pm$ 89.5	152.1 $\pm$ 83.7	135.7 $\pm$ 73.3
Early drink	182.6 $\pm$ 85.7	176.1 $\pm$ 78.2	154.7 $\pm$ 68.8
Late drink	217.1 $\pm$ 112.6	209.5 $\pm$ 109.9	120.9 $\pm$ 92.6
Early drug	163.3 $\pm$ 93.8	150.7 $\pm$ 95.1	149.4 $\pm$ 76.6
Late drug	152.9 $\pm$ 100.7	132.8 $\pm$ 98.4	179.1 $\pm$ 111.6

t - tests for paired observations: df = 6

#### HORLICKS:

##### a) Mean level 2300h - 0130h

Baseline v early drink t = 0.69 (n.s.)

Baseline v late drink t = 1.97, p < 0.05, 1-tailed

##### b) Mean level 2300h - 0400h

Baseline v early drink t = 1.07 (n.s.)

Baseline v late drink t = 2.30, p < 0.05, 1-tailed

##### c) Mean level 2300h - 0630h

Baseline v early drink t = 0.90 (n.s.)

Baseline v late drink t = 2.23, p < 0.05, 1-tailed

#### NITRAZEPAM:

No significant differences were found between the baseline values and either early or late drug results (2-tailed level).



TABLE 4.5. THE EFFECTS OF BEDTIME EATING ON THE NOCTURNAL COMPOSITION OF PLASMA.

Individual subjects' plasma triglyceride levels before and during Horlicks administration.

Each value is the subject's mean  $\pm$  S.D. plasma triglyceride (TG) level (mg/100ml plasma) over the particular 2½h sector of the night. The majority of values for each of 7 subjects are the mean of 5 estimations.

Subjects	Sector of night (hours on clock)	Mean TG level (mg/100ml plasma)		
		Baseline level	Early drink	Late drink
MC		178.1 $\pm$ 33.7	196.8 $\pm$ 14.7	249.0 $\pm$ 27.0
JG		291.4 $\pm$ 14.7	212.0 $\pm$ 21.7	255.2 $\pm$ 32.9
GJ	2300h	290.5 $\pm$ 31.5	340.0 $\pm$ 4.5	408.8 $\pm$ 6.3
DJ	to	81.4 $\pm$ 13.7	157.8 $\pm$ 13.8	132.2 $\pm$ 17.9
RMcD	0130h	105.2 $\pm$ 23.3	140.0 $\pm$ 14.1	95.8 $\pm$ 11.5
JR		129.7 $\pm$ 11.2	171.6 $\pm$ 5.6	271.4 $\pm$ 72.7
MT		98.9 $\pm$ 27.4	58.0 $\pm$ 3.6	107.3 $\pm$ 17.5
Mean $\pm$ S.D.		167.9 $\pm$ 89.5	182.3 $\pm$ 85.6	217.1 $\pm$ 112.7
MC		124.8 $\pm$ 39.2	170.2 $\pm$ 18.4	207.8 $\pm$ 10.8
JG		123.6 $\pm$ 14.6	139.0*	253.3 $\pm$ 30.4
GJ	0130h	271.2 $\pm$ 30.3	322.3 $\pm$ 24.0	413.3 $\pm$ 11.6
DJ	to	85.9 $\pm$ 9.7	164.4 $\pm$ 21.8	165.0 $\pm$ 19.7
RMcD	0400h	111.1 $\pm$ 23.4	149.5 $\pm$ 16.6	100.0 $\pm$ 7.1
JR		272.2 $\pm$ 46.4	217.6 $\pm$ 10.2	222.6 $\pm$ 27.3
MT		75.9 $\pm$ 21.1	69.7 $\pm$ 7.5	104.8 $\pm$ 13.6
Mean $\pm$ S.D.		152.1 $\pm$ 83.7	176.1 $\pm$ 78.2	209.5 $\pm$ 109.9
MC		104.0 $\pm$ 7.0	155.0 $\pm$ 3.6	127.6 $\pm$ 3.8
JG		209.2 $\pm$ 29.9	139.5 $\pm$ 10.5	115.2 $\pm$ 14.8
GJ	0400h	263.6 $\pm$ 22.9	278.4 $\pm$ 38.8	317.0 $\pm$ 13.5
DJ	to	70.4 $\pm$ 15.9	132.2 $\pm$ 27.4	36.4 $\pm$ 1.8
RMcD	0630h	113.9 $\pm$ 41.8	96.4 $\pm$ 11.0	79.2 $\pm$ 3.5
JR		120.0*	206.3 $\pm$ 19.1	112.8 $\pm$ 9.3
MT		68.9 $\pm$ 10.2	75.2 $\pm$ 4.1	58.0 $\pm$ 15.6
Mean $\pm$ S.D.		135.7 $\pm$ 73.3	154.7 $\pm$ 68.8	120.9 $\pm$ 92.6

\* Only one sample taken from this subject in this sector of the night owing to technical difficulties.

TABLE 4.6. THE EFFECTS OF BEDTIME EATING AND OF NITRAZEPAM ON THE NOCTURNAL COMPOSITION OF PLASMA.

Lack of correlation between the total min of slow wave sleep (stages 3+4) accumulated in the first 6h of sleep and the nocturnal growth hormone output integrated over the first 6h of sleep.

The slow wave sleep (SWS) data for each baseline blood night is paired with the corresponding growth hormone (GH) data for each of 7 subjects.

Subjects	Baseline blood nights			
	Pre-food drink blood night		Pre-drug blood night	
	Mean min SWS in 1st 6h sleep	Integrated GH output	Mean min SWS in 1st 6h sleep	Integrated GH output
MC	27.8	30.8	12.1	30.8
JG	72.9	7.0	32.3	7.4
GJ	102.7	37.6	88.8	21.0
DJ	89.3	22.2	74.6	16.2
RMCD	150.8	38.2	67.1	25.4
JR	48.1	29.6	57.1	22.6
MT	99.4	32.8	107.6	7.6

Correlation coefficient (r) between min of SWS and the integrated GH output on:

(a) Pre-food drink blood night:  $r = 0.35$ ,  $df = 5$  (n.s.)

(b) Pre-drug blood night:  $r = -0.42$ ,  $df = 5$  (n.s.)



# CHAPTER 5

## THE EFFECTS OF DIFFERENT FORMS OF BEDTIME NOURISHMENT ON SLEEP

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## CHAPTER 5

### SUMMARY

16 middle-aged subjects had their sleep recorded for five nights under each of four conditions of bedtime intake:

A placebo capsule, milk, Horlicks and a drink formulated to be nutritionally equivalent to Horlicks but containing no milk or cereal.

None among the three food drinks had any significant effect on sleep when compared with sleep after the capsule, but Horlicks was associated with significantly less broken sleep than either of the other two food drinks.

## INTRODUCTION

In Chapter 2, I reviewed a number of papers which indicated that bedtime nutrition can influence sleep and in particular that a combination of milk and cereal taken prior to sleep may lead to a less restless night than after other forms of nourishment (Laird and Drexel, 1934; Kleitman et al., 1937). The proprietary brand of malted milk and cereal food drink, Horlicks, is such a combination and earlier studies indicated that when taken prior to bedtime, it too, diminished the amount of restlessness through the night (Southwell et al., 1972), reduced the min of waking interrupting sleep and extended the total duration of sleep (Březinová and Oswald, 1972). In neither of these two recent studies was a comparison made between Horlicks and any other form of nourishment. The obvious comparison is between Horlicks and milk, as Horlicks powder is normally added to milk. Březinová and Oswald considered this comparison but rightly discarded the idea on the grounds that had no difference in sleep been found after milk compared with Horlicks, then they would not have known whether neither nor both were influencing sleep. In the light of the studies referred to above, the equivocal results of others (Giddings, 1934) and the negative/

negative results reported by Hamilton et al. (1966) and by me in Chapter 3, Part 3, it was of interest to undertake a further study of the influence of bedtime eating on sleep. In view of the lack of effect of Horlicks on the sleep of subjects whose food intake was not limited in any way (Chapter 3), I decided to revert to the more controlled experimental approach and to restrict my subjects' evening eating and drinking to before 1900h, as Březinová and Oswald (1972) had done.

This experiment was designed to investigate a number of questions which have arisen out of the previous studies into nutrition and sleep, e.g.

- (1) Are different forms of nourishment better than nothing to eat at bedtime in reducing waking through the night?
- (2) Is a milk and cereal combination at bedtime (in the form of Horlicks) better than milk alone in promoting a less broken and longer lasting sleep period?
- (3) Would a food drink having an identical basic composition of carbohydrate, fat, protein and contributing an equal number of calories, but not made from any cereal or dairy products, differ from Horlicks in its influence on subsequent sleep?



## METHODS

### (a) Subjects and treatments

Sixteen healthy volunteers of mean age 59 years (range 52 to 67) took part in the experiment. They were asked not to take any alcohol and to keep their times of going to bed and of arising in the morning as constant as possible. In addition, subjects were instructed not to eat or drink anything after 1900h, except the treatment given them, for the 15 weeks that each was involved in the experiment.

The four treatments compared were:

- (A) A yellow placebo capsule taken with a little water. This treatment was to represent the no bedtime nourishment condition. Subjects were told that the capsules contained a herbal preparation, which would help them sleep.
- (B) Flavoured drink, a powdered mixture (specially formulated by Beecham Products Ltd of soya flour, dried whole egg and glucose syrup solids, which when mixed with 250ml of hot water, was equivalent in energy (1260KJ or 300kcal), protein (12.8g), carbohydrate (34.9g) and fat (12.1g) content to treatment (D), Horlicks.
- (C) /

(C) Whole fresh milk (280ml) estimated to be equivalent to 800KJ or 190 kcals.

(D) 'Horlicks' powder, a proprietary brand of malted barley, wheat flour and triple concentrated full cream milk. 30g of the powder was mixed with 250ml of fresh whole milk which together contained about 1260KJ or 300 kcals.

Treatments (B), (C) and (D) were all made up as hot drinks and taken by the subjects at the temperature they preferred.

(b) Experimental design.

Each of the 16 subjects took all four treatments during the 15 weeks they were involved in the experiment. The order they took the treatments was according to a 4 x 4 Latin square design:

Treatment order				Subjects			
B	A	D	C	A.W.	J.R.	M.T.	G.J.
C	D	B	A	M.W.	J.G.	R.McD.	M.S.
D	C	A	B	A.H.	G.H.	F.C.	R.R.
A	B	C	D	K.B.	W.H.	M.C.	F.W.

Subjects attended the laboratory in pairs, always differing in the treatment they received, starting with the first pair A.W. and M.W. and so on down each row finishing with pair R.R. and F.W. Each treatment was taken at about 2200h every night for a total of 21 nights.

The/

The experimental design was such that subjects took each treatment at home every night for 15 days before coming to the sleep laboratory to be recorded electrophysiologically on six consecutive nights. On each laboratory night subjects had nine silver disc electrodes attached to their skin. Two pairs of electrodes above and below the outer canthi of the eyes recorded two channels of electro-oculogram (EOG), two parieto-occipital electrodes gave a channel of electroencephalogram (EEG) and two submental electrodes measured muscle tone (EMG). The ninth electrode served as an earth. Recordings began at 2215h<sup>±</sup> 15 min and terminated at 0700h<sup>±</sup> 15 min. The times for lights-off and for arising in the morning for each pair were selected to fit in with work commitments and their usual pattern of life, but all subjects were recorded for an equal length of time i.e. 8.75h and for any pair of subjects the times for lights on and off were kept the same on all 24 attendances at the sleep laboratory. Subjects slept in comfortable beds in sound-attenuated bedrooms and the temperature was thermostatically controlled. The laboratory bedrooms have no windows, but a dimmer switch on the bedroom lights allowed volunteers to have some light if they so wished. At the beginning of the experiment subjects were asked what/



what type of bedding they preferred, either blankets or continental feather quilts and on all nights at the laboratory they had the same bedding.

For each treatment the experimental design was:

- |               |  |
|---------------|--|
| Weeks 1 and 2 | Subjects took their treatment on each of 15 nights at home               |
| Week 3        | 1 adaptation night and 5 recording nights at the laboratory on treatment |
| Week 4        | At home - no treatment   |

The above four week regime was repeated for each of the three other treatments except the last when week 4 was not included, making 15 weeks in all. The six consecutive nights at the sleep laboratory were always Monday to Saturday. The Monday nights were for adaptation and have not been included in the results. On the first and last nights of attendance on each treatment subjects were weighed in light indoor clothing on a beam balance by the experimenter. Their weights (in stones and lbs) were obtained by moving the poises along the weighing beam until it was hanging horizontally and the positions noted to the nearest  $\frac{1}{4}$  lb. Each subject was thus weighed on eight occasions.

Only once during a six-night run was a subject unable to attend owing to illness. On that occasion the subject continued to take his treatment until the following week when, after another adaptation night, the missing recordings were made.

(c) Reading of electrophysiological records.

The 20 electrophysiological recordings made for each subject were coded by another person so that when the records were read at the end of the experiment, the scorer was unaware of the experimental condition. The criteria of Rechtschaffen and Kales (1968) was used to score the records. In the case of one subject (subject M.C.) the minimum voltage requirement for stages 3+4 was reduced from 75uV to 40 uV. This 60 year old subject had periods of slow waves which were quite distinct from stage 2 but never attained the 75uV criteria for slow wave sleep.

The records were read visually by me, page by page and categorized into the various sleep stages according to the criteria above. This sequence of sleep stages and page numbers were then punched on to computer cards and with the aid of a computer programme these raw scores were converted into the number of min awake and in each of the sleep stages (1,2,3,4 and REM sleep) in the accumulation of each successive hour of sleep.

Wakefulness was treated as intruding into sleep and was not included in the calculation of each successive hour of sleep, so it may take more than 60 min on the 'clock' to achieve one hour of sleep, e.g. it/

it may take 130 min on the clock to accumulate 60 min of sleep if 70 min of wakefulness interrupted that hour of sleep. The 70 min could be one or many periods of waking. Wakefulness such as this, which occurs within sleep is termed 'intervening wakefulness', to differentiate it from wakefulness occurring before the onset of sleep or after the sleeping period has ended in the morning and before the recording has finished. The latter will be called 'morning wake-time'. The computer programme also calculated the total time the subject was asleep during the recording - total sleep time, how long it took him/her to fall asleep after the recording began - sleep onset latency, the latency from sleep onset to the first appearance of REM sleep - REM latency, and the number of times that the subject's sleep shifted from any stage of sleep to another particular stage of sleep or wakefulness, in each successive hour of sleep.

(d) Calculations using sleep data.

(i) Whole night measures

For each individual subject the mean of the 5 recorded nights on each treatment was calculated for total time asleep, latency to sleep onset, latency to the first appearance of REM sleep, the total amount of time spent awake after first falling asleep and until lights/



lights on in the morning (intervening wakefulness plus morning wake-time), the mean total min spent in each of the sleep stages 1,2,3,4 and REM. The mean total number of times that a subject awoke or shifted sleep stage into stage 1 while taking each treatment was also calculated.

Grand means for each of the four treatments were obtained by averaging the 16 individual mean scores for each treatment. This procedure was carried out for all the whole-night sleep measures listed above. For statistical analysis of these whole-night measures I employed data in the form of the subject's individual mean totals for each treatment.

(ii) Hour/hour analysis of sleep data.

The computer printed out an analysis of the number of min spent in each of the sleep stages 1,2,3,4 and REM, and the number of shifts of sleep stage to stage 1 and awake in each successive 60 min period of accumulated sleep.

Intervening wakefulness, as described earlier, was treated as an interruption of sleep and was calculated in terms of the min of wakefulness which occur in the accumulation of each successive hour of sleep. The amount of time spent in each of the sleep stages/

stages, wakefulness and the number of shifts of sleep stage in each hour of accumulated sleep was analysed by collecting together the data from all 16 subject-nights for each of the nights: capsules 1,2,3,4 and 5 and similarly for the other sets of five nights for the three other treatments. In this way all 16 subjects first, second, third and so on hours of sleep on each particular night of a treatment were brought together. This was carried out for all the sleep measures listed above. Thereafter, the mean number of min were calculated for each of the sleep measures, for the first, second, third and so on hours of sleep.

Most subjects achieved at least six hours of sleep on treatment nights, however, when an individual subject slept for less than six hours, the following procedure was carried out. For example, if the subject slept for 5h 45min then his sleep data for the incomplete sixth hour of sleep was included in the sixth hour total for all 16 subjects. When the mean for the sixth hour was calculated the division would be by 15.75 instead of 16. If several subjects failed to sleep for six complete hours, then the divisor was calculated by adding the number of complete sixth hours plus all the decimal fractions of an hour and then dividing the grand total min of the particular sleep stage measured in that sixth hour by the calculated divisor.

For/

For statistical purposes a different method of extrapolation had to be employed. The statistical tests used in the analysis of this data involved the comparison of individual subjects' means, for example, when the amounts of intervening wakefulness interrupting the first 6h of accumulated sleep were compared among conditions, the individual totals of intervening wakefulness were added up for the first 6h of sleep on each of 20 nights for each subject. If on any night a subject did not achieve 6h of sleep then the total he achieved was extrapolated to 6h, e.g. if a total of 40 min of wakefulness interrupted a total night's sleep of 5h 30 min then this was extrapolated to 6h of sleep by multiplying 40 min by  $\frac{6}{5.5} = 43.6$  min. This method of extrapolating intervening wakefulness was considered superior to merely extrapolating the final incomplete hour of sleep to 1 hour. Similar extrapolations were done, where necessary, for min in stage 1 and 2 and shifts of sleep stage to awake plus shifts to stage 1. If a subject did not achieve 6h of sleep then the amount of REM sleep in the first 6h of sleep was obtained by extrapolating the min of REM sleep in hours 4 to 6 of sleep and adding this to the min recorded in hours 1 to 3. This method was employed because the majority of REM sleep occurs in the/



the later night. No extrapolation procedure was employed for SWS as it mostly occurs in the early night and so for nights when less than 6h of sleep were achieved the individual's whole night total for min in SWS was used in the calculations.

Thereafter, the results from the five nights on each treatment were averaged for each subject and these individual means used in the statistical tests.

(e) Subjective ratings.

During the entire experimental period subjects rated their daytime anxiety and in the morning made an assessment of the quality of their sleep and how alert and refreshed they felt after that night's sleep. Subjective ratings were made using analogue scales, where ratings were made by putting a mark on a 100mm line. The mid-point on the line was to represent their 'average' state and deviations from usual as marks to the left or right of the mid-point. The mid-point was a hypothetical point on the line and its position was not indicated. Sleep quality ranged from 'worst ever' on the extreme left end of the line to 'best ever' on the extreme right hand end of the line. The subjective anxiety rating form was similarly designed such that an extremely anxious state/

state was represented by the left hand end of the line and an extremely calm state by the right hand end, whereas the subjective rating form to assess morning vigilance had its extreme poles reversed so that the more 'positive' state of alertness was placed at the left side and the more 'negative' feelings of sluggishness were represented by the right hand side of the line.

The distance from the left hand end of the line to the mark made by the subject was subsequently measured in mm. The mean subjective rating in mm was calculated for each subject for the 15 days that he/she was taking the treatment at home prior to attending the sleep laboratory. The mean ratings were also calculated for the six days when they slept at night in the laboratory and the mean total of the 21 consecutive days over which a subject took a treatment were also calculated and this was done for all four treatments. The individual mean scores were used for statistical analysis. Subjective ratings were also collected for continuity during weeks 4,8,12 of the experiment when subjects slept at home and took no treatment but these ratings were not included in the calculations.

### STATISTICAL ANALYSIS

The approach I used in the statistical analysis of this study is best explained in conjunction with the table below which summarizes the attributes of bedtime nutrition that were to be compared:-

	(i) Contains calories	(ii) Contains milk and cereal	(iii) Contains about 300 calories
Capsules	NO	NO	NO
Flavoured drink	YES	NO	YES
Milk	YES	NO	NO
Horlicks	YES	YES	YES

As mentioned in the Introduction of this chapter, the previous studies into the influence of food on sleep generated certain questions, e.g.

(a) Does bedtime nutrition improve sleep? To investigate this, I compared the results from each of the three bedtime food drinks, in turn, with capsules using correlated t-tests (Ferguson, 1959).

(b) Does the number of calories make any difference? Comparison between Horlicks and milk were carried out, again using correlated t-tests.

(c) Does the source of the calories matter? To investigate this I compared the 150-caloric food drinks, Horlicks and flavoured drink, using correlated t-tests.

Evidence from the literature suggested the prediction that bedtime nourishment in the form of milk and cereal would be more likely to improve subsequent sleep than other forms of nourishment and thus a 1-tailed level of/



of significance could justifiably be used for comparisons between Horlicks and each of the other bedtime treatments.

Three specific predictions were made:-

- (1) That Horlicks would be better than capsules was predicted from both the Brezinová and Oswald (1972) study and Kleitman et al. (1937).
- (2) That Horlicks would be better than milk was predicted from Kleitman et al. (1937).
- (3) That Horlicks would be better than flavoured drink was predicted from both Laird and Drexel (1934) and Kleitman et al. (1937).

I realise that if many t-tests are carried out then the probability of getting a significant result by chance alone, is increased, i.e. the probability of at least one comparison out of three being significant at the 5% level by chance alone is 14.26%. The probability of two out of three reaching the 5% level of significance by chance is 0.725% and the probability of all three of my predictions being significant at the 5% level by chance alone is negligible, i.e. 0.0125%.

Two other comparisons were made, i.e. sleep after milk with sleep after capsules and sleep after flavoured drink compared with sleep after capsules. No specific prediction was made for either comparison but evidence from the Kleitman et al. (1937) study suggests that sleep after milk would not be significantly different from sleep after the inert capsule.

## RESULTS

### (I) Electrophysiological recordings

#### (a) Comparison of each of the food drinks with capsules.

##### (i) Whole night measures.

There were no significant differences in the mean total time that subjects were asleep when any one of the food drinks had been taken at bedtime in comparison with their sleep after capsules (Table 5.1). Similarly, there were no significant differences between any of the three bedtime drinks when compared with capsules in the mean total min of wakefulness occurring after the first onset of sleep and before the end of the recording in the morning (Table 5.2).

The mean total number of min spent in stage 1 sleep, stage 1 sleep plus total wakefulness after sleep onset, sleep stage 2, stages 3+4 and REM sleep were unchanged by taking any of the three bedtime food drinks when compared with the distribution of sleep during the nights recorded when the capsules were being taken (Tables 5.3; 5.4; 5.5; 5.6 and 5.7 respectively).

##### (ii) Totals accumulated in the first 6h of sleep.

The mean min spent awake in the accumulation of the first 6h of sleep were not significantly different when the results from each of the food drinks were compared with the means of the nights when subjects had the capsules (Table 5.8). Neither were the results significantly/

significantly different when the min of intervening wakefulness were combined with the min spent in stage 1 (drowsiness) (Table 5.9).

Flavoured drink tended to impair sleep, compared with capsules, in that intervening wakefulness and intervening wakefulness plus stage 1 were increased. However, this was not significant (Tables 5.8; 5.9).

Bedtime nutrition did not appear to influence the mean min of stages 3+4 (Table 5.10) or mean min of stage REM sleep in the accumulation of the first 6h of sleep (Table 5.11), when each of the three bedtime drinks was compared with capsules.

The mean number of times that subjects shifted their sleep stage into stage 1 or awake in the first 6h of sleep were combined and together were found not to differ significantly between the four bedtime treatments (Table 5.12).

(iii) Totals accumulated in the first 3h of sleep.

Comparisons between the mean min of intervening wakefulness (Tables 5.13 and 5.14) stages 3+4 (Table 5.10) and stage REM (Table 5.15) accumulated in the first 3h of sleep did not differ significantly when the results from each of the three bedtime food drinks were compared with those recorded during the administration of the capsules.



(b) Comparison of the three bedtime drinks with each other.

(i) Whole night measures

There were no significant differences between the three bedtime drinks in the mean total min spent asleep (Table 5.1). Horlicks compared with flavoured drink was associated with fewer total min awake between the first onset of sleep and the end of the recording (Table 5.2) and less stage 1 plus total min waking after sleep onset (Table 5.4) but because in both cases only one out of three of my predictions was fulfilled, only the latter comparison was considered to be significant.

The three bedtime food drinks did not differ in the mean total min spent in stage 1 (Table 5.3), stage 2 (Table 5.5), stages 3+4 (Table 5.6) or stage REM sleep (Table 5.7) accumulated during the whole night.

(ii) Totals accumulated in the first 6h of sleep.

Horlicks at bedtime significantly reduced intervening wakefulness (Figure 5.1 and Table 5.8) and intervening wakefulness plus stage 1 (Figure 5.2 and Table 5.9) in the first 6h of sleep when compared with both flavoured drink and with milk. The mean min spent in slow wave sleep (stages 3+4) (Table 5.10) and REM sleep (Table 5.11) in the first 6h of sleep did not/

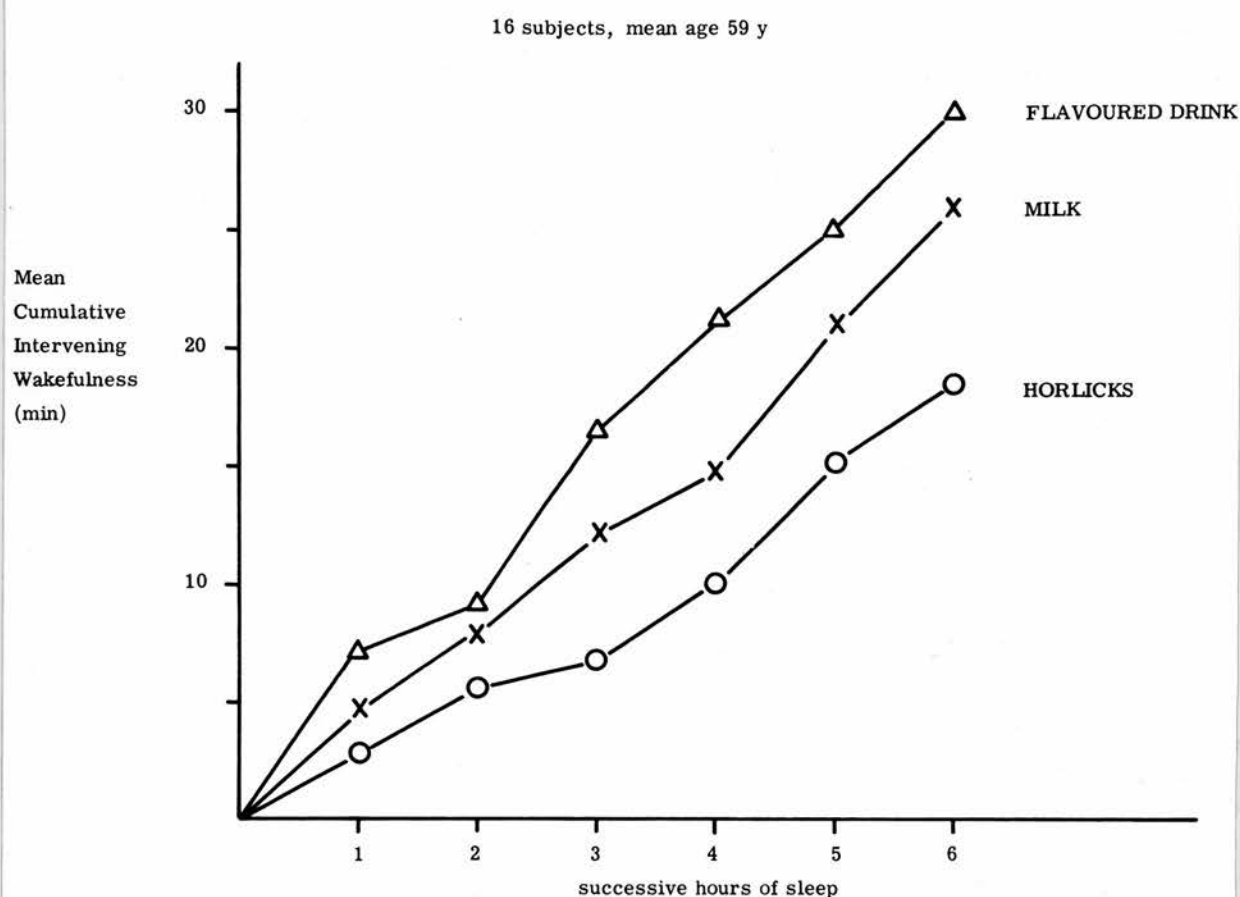


FIGURE 5.1 Mean cumulative min of intervening wakefulness occurring in the first 6h of sleep in 16 middle-aged subjects.

Each subject was recorded for 5 nights under each condition.

Statistical analysis and a measure of the inter-individual variance in Table 5.8.

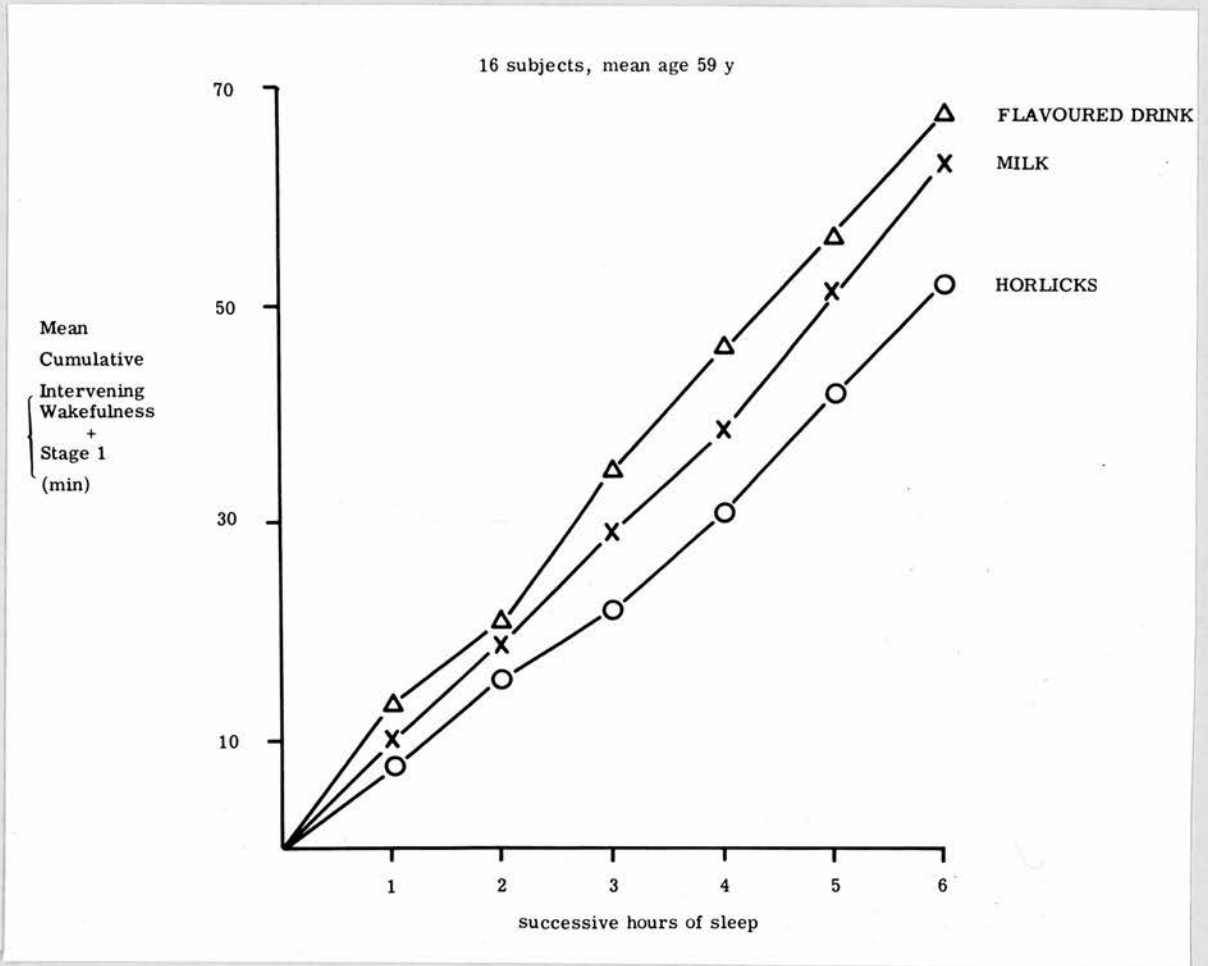


FIGURE 5.2 Mean cumulative min of intervening wakefulness combined with the mean cumulative min of stage 1 (drowsiness) in the first 6h of sleep in 16 middle-aged subjects.

Each subject was recorded for 5 nights under each condition.

Statistical analysis and a measure of the inter-individual variance in Table 5.9.



not differ among the three bedtime food drinks. Neither did the mean number of transitions of sleep stage into stage 1 plus shifts to wakefulness in the first 6h of sleep differ significantly among the three food drinks (Table 5.12).

(iii) Total intervening wakefulness occurring in the first 3h and second 3h of accumulated sleep.

The improvement in sleep, when Horlicks had been taken at bedtime, appeared to be greater in the first 3h of sleep than the second 3h. Intervening wakefulness after Horlicks when compared with both milk and flavoured drink was reduced more during the early hours of sleep than in the later half (Tables 5.13; 5.14). No prior prediction to this effect had been made and so 2-tailed tests were employed. The comparison between Horlicks and flavoured drink for the first 3h totals only reached the 5% level of significance and thus was not considered to be significant.

(II) Subjective Measures

No significant differences were found for any of the mean subjective ratings among the four experimental treatments (Tables 5.16; 5.17; 5.18). This was true if the data was in the form of the means of the entire 21 days on each treatment, the 15 days on each treatment at home prior to attending the sleep laboratory, or if only the six laboratory nights alone were considered.

(III) Body Weight Measurements

Table 5.19 illustrates that subjects' body weights changed little over the 13 weeks of attendances at the sleep laboratory (the greatest S.D. being  $\pm$  2.46 lb).

## DISCUSSION

Older subjects were selected to take part in this study for the same reason indicated in the previous Chapters, namely, on average they do not sleep as well as younger people and thus there is more scope for improving their sleep.

Březinová and Oswald (1972) suggested that the beneficial effect of Horlicks on sleep increased with serial administration and because of this, I asked my subjects to take a treatment every evening for the 15 days preceding the six attendances at the laboratory. In addition this regime meant that the sleep recordings were made when subjects were used to taking their treatment and any novelty value of a treatment would be diminished. However, this design may also have reduced any likelihood of showing that sleep after a bedtime snack would be less broken than sleep after an acaloric capsule and so if some subjects had found that they felt hungry during the night in the 'at home' period on capsules they could adapt their eating pattern by having an unusually large evening meal to compensate for the lack of an evening snack without breaking the "no eating/drinking after 1900h" rule. I am however, confident that they did not break this latter instruction.

The/



The subjects were weighed frequently during the study because changes in body weight have been associated with changes in the nightly duration of sleep. Crisp et al. (1973), reported that obese patients slept less as they lost weight and Crisp et al. (1971) and Lacey et al. (1975) found that anorexia nervosa patients slept longer as their weight was regained. Further evidence for this relationship was revealed in a study that involved interviewing 375 psychiatric out-patients where Crisp and Stonehill (1973) found on correlation analysis of the answers that a report of loss of body weight was associated with shorter sleep duration and that a gain in weight correlated with an increased amount of sleep. Fortunately, there were only small fluctuations in the weights of my subjects and so changes in weight were unlikely to have contributed appreciably to the changes in sleep.

The results from the recordings of sleep were not completely as expected in that the comparisons between each of the food drinks with capsules showed no significant differences on any of the measures investigated. Looking at the results from 20 nights I noticed that some subjects did consistently sleep better after milk or Horlicks compared with capsules, whereas/

whereas others slept best after capsules, and certainly during the experiments some of the subjects said they felt hungry on the nights they had capsules, whereas others complained of feeling over-full after half-a-pint of food drink. This led me to think that the usual dietary habits of subjects must, in part, determine whether their sleep is improved or disrupted by taking food at bedtime. The next Chapter (6) is about my attempts to clarify this problem and I discuss it in more detail there.

In retrospect, it appears that the original intention of the experiment, which was to compare the effects on sleep of four different types of bedtime nutrition, was complicated by the fact that the form of presentation of the four treatments were not comparable, i.e. the three types of bedtime food were taken as hot liquids whereas the no nourishment condition was a capsule.

Comparisons between Horlicks and the other two food drinks (flavoured drink and milk) did reveal significant differences on measures of the disruption of sleep by waking. Presumably, this is because the factor of dietary habit is reduced, in that all three drinks comprised half a pint of warm, nourishing liquid and so might be considered equally good or bad depending on bedtime nutritional predilections. Thus/

Thus any differences in their effects on sleep were more likely to be due to differences in their nutritional content and so the following tentative conclusions are made, based on the comparisons between Horlicks and each of the two bedtime drinks:

Flavoured drink tended to impair sleep, although not significantly. Soya products are perhaps unfamiliar to subjects or they could have caused gastrointestinal distress by increasing the flatus volume (Rackis, 1974).

Interruptions of sleep by periods of waking were less after Horlicks than after either flavoured drink or milk. The superiority of Horlicks over flavoured drink suggests that the source of calories is important for the effects on sleep, for flavoured drink and Horlicks contained the same number of calories and percentages of protein, carbohydrate and fat. However this conclusion must be tempered by the suggestion above that the flavoured drink may be less easily digested. Laird and Drexel (1934) found that an easily digested milk and cereal snack at bedtime was associated with fewer body movements during subsequent sleep than after a less easily digested snack at bedtime. The differences I found in sleep after Horlicks and after flavoured drink are thus comparable to/



to their findings. Several of the subjects complained that they did not like the taste of the flavoured drink and so palatability may also be a factor in this comparison.

The comparison between Horlicks (made up with milk) and milk showed that there was less intervening wakefulness when Horlicks had been taken at bedtime. In retrospect it would have been of interest to have made milk and Horlicks iso-energetic by enriching the milk with the equivalent of about 100 calories of either powdered or condensed milk.

No effects of bedtime nutrition were found on the min accumulated of either slow wave sleep or REM sleep, whether the first 3h, 6h or total sleep time were considered. Phillips et al. (1975) suggested that changes in the carbohydrate and fat content of the diet might influence the total amount of REM sleep in that a high carbohydrate/low fat diet was associated with higher levels of REM sleep than a low carbohydrate/high fat diet. The diets were iso-energetic and the percentages of protein were the same. However, they altered the entire daily intake of food, whereas I only altered a relatively small part, amounting to no more than 300 calories of the daily intake.

Siegel (1975) found that the amount of REM sleep that cats accumulated during daytime sleep was negatively/

negatively correlated with the amount of food that the cat ate during the following 12h. In my experiment, taking food at bedtime did not appear to reduce the amount of REM sleep when food-drink nights were compared with nights after capsules, however no measure was made of the food intake of subjects over the days that they came to the laboratory at night and subjects may have been consciously reducing or increasing their daytime intake depending on which treatment they were to take at bedtime, and thus subjects' overall caloric intake would be little affected. It would be very interesting to see if there was a relationship between the amount of REM sleep at night and the next day's caloric intake in man. I suspect that social cues may be more important than internal ones in humans, but it might be possible to detect a relationship in babies on a "feeding on demand" schedule where their internal drives determine their food intake.

To conclude, in some subjects, sleep appeared to be less broken after either milk or Horlicks when compared with sleep after capsules, whereas other subjects slept better after capsules (or worse after food at bedtime, depending on your point of view) and because of this all the comparisons between the food drinks/

drinks and capsules were insignificant. I speculated that differing dietary habits among the subjects was responsible for this and thus comparisons between Horlicks and the other two bedtime food drinks were made in order to study the effects on sleep of differing nutritional composition and energy content. The comparisons of Horlicks with flavoured drink and with milk demonstrated that sleep after Horlicks was less broken than after either of the other two drinks and so possibly the amount and the source of calories does matter. However, some subjects found the flavoured drink unpleasant and so palatability may also be a factor.

I had made three predictions. One prediction that sleep after Horlicks would be less broken by wakefulness than sleep after capsules, was not confirmed. However, the two other predictions that sleep after Horlicks would be less broken than after either milk or flavoured drink, were both confirmed. Probability theory showed that the likelihood of two out of three predictions reaching a  $p < 0.05$  criterion by chance alone, is remote.



TABLE 5.1. COMPARISON OF FOUR BEDTIME TREATMENTS: WHOLE NIGHT MEASURES. Mean total time asleep (min). Each value for each of 16 subjects is the mean of 5 consecutive nights.

Subjects	Mean min total sleep time			
	Capsules	Flavoured drink	Milk	Horlicks
KB	441.0	457.6	439.0	442.3
MC	412.5	392.5	361.7	371.9
FC	475.5	481.3	488.2	477.7
JG	426.3	433.8	477.1	429.6
GH	458.4	465.6	476.1	487.8
AH	470.0	461.0	486.1	477.6
WH	448.7	439.9	466.2	444.3
GJ	499.2	501.3	505.2	504.3
RMCD	435.7	387.6	466.6	465.5
JR	422.4	433.0	441.7	442.4
RR	495.6	457.7	491.6	496.6
MS	454.4	429.7	414.2	437.7
MT	446.3	420.8	456.0	453.1
FW	473.4	428.7	453.8	459.8
AW	452.0	488.7	482.8	476.6
MW	470.1	468.8	402.6	435.3
Mean	455.1	446.8	456.8	456.4
<sup>+</sup> S.D.	<sup>+</sup> 24.8	<sup>+</sup> 32.0	<sup>+</sup> 37.8	<sup>+</sup> 32.1

t-tests for paired observations between planned comparisons: df = 15 (2-tailed).

	Flavoured drink	Milk	Horlicks
Capsules	t = 1.42 (n.s.)	t = 0.22 (n.s.)	t = 0.26 (n.s.)
Flav. drink	-	-	t = 1.43 (n.s.)
Milk		-	t = 0.09 (n.s.)

TABLE 5.2 COMPARISON OF FOUR BEDTIME TREATMENTS: WHOLE NIGHT MEASURES.

Mean total min of wakefulness occurring between the first onset of sleep and the end of the recording. Each value for each of 16 subjects is the mean of 5 consecutive nights.

Mean total wake time after sleep onset (min)				
Subjects	Capsules	Flavoured drink	Milk	Horlicks
KB	33.0	20.7	41.2	31.9
MC	81.6	88.6	106.8	111.5
FC	27.9	18.8	15.9	23.4
JG	90.5	81.3	29.0	87.7
GH	32.4	42.5	41.4	12.1
WH	55.1	56.3	33.8	49.7
AH	19.8	24.0	9.9	12.8
GJ	15.2	15.0	9.0	8.3
RMCD	70.7	107.4	42.7	45.0
JR	49.6	36.3	37.6	38.3
RR	11.8	47.1	11.2	6.8
MS	57.0	83.3	92.8	75.9
MT	49.0	84.6	52.6	53.4
FW	29.2	72.7	32.0	39.6
AW	57.8	22.6	25.0	29.5
MW	25.8	29.4	65.4	40.4
Mean	44.2	51.9	40.4	41.6
$\pm$ S.D.	$\pm 23.6$	$\pm 30.3$	$\pm 28.0$	$\pm 29.5$

t-tests for paired observations: df = 15.

	Flavoured drink	Milk	Horlicks
Capsules	t = 1.40(n.s.)	t = 0.58(n.s.)	t = 0.64 (n.s.)
Flav. drink	-	-	t = 1.78, p < 0.05*
Milk		-	t = 0.26 (n.s.)

\*not significant.

TABLE 5.3. COMPARISON OF FOUR BEDTIME TREATMENTS: WHOLE NIGHT MEASURES

Mean total min stage 1 accumulated during the whole night. Each value for each of 16 subjects is the mean of 5 consecutive nights.

Subjects	Mean total min of stage 1			
	Capsules	Flavoured drink	Milk	Horlicks
KB	36.8	49.1	45.7	42.5
MC	80.9	76.3	65.4	71.8
FC	48.2	47.8	39.2	43.4
JG	37.2	45.3	60.5	43.4
GH	27.2	28.1	31.7	32.5
WH	91.2	81.2	82.0	80.3
AH	45.4	39.2	41.7	37.8
GJ	45.1	42.7	57.3	46.4
RMcD	39.9	35.9	37.5	47.6
JR	47.9	53.3	47.1	40.9
RR	42.0	60.5	51.6	47.0
MS	34.0	33.5	42.8	30.9
MT	33.6	45.4	48.8	46.4
FW	52.7	67.5	53.9	51.0
AW	50.3	47.5	47.8	45.2
MW	37.9	45.8	39.3	41.4
Mean	46.9	49.9	49.5	46.8
± S.D.	± 16.8	± 14.8	± 12.3	± 12.7

No significant differences between treatments



TABLE 5.4. COMPARISON OF FOUR BEDTIME TREATMENTS: WHOLE NIGHT MEASURES  
Mean total min of wakefulness and stage 1 combined occurring between  
the first onset of sleep and the end of the recording. Each value  
for each of 16 subjects is the mean of 5 consecutive nights.

Mean total min of waking and stage 1 combined				
Subjects	Capsules	Flavoured drink	Milk	Horlicks
KB	69.8	69.8	86.9	74.4
MC	162.5	164.9	172.2	183.3
FC	76.1	66.6	55.1	66.8
JG	127.7	126.6	89.5	131.1
GH	59.6	70.6	73.1	44.6
WH	146.3	137.5	115.8	130.0
AH	65.2	63.2	51.6	50.6
GJ	60.3	57.7	66.3	54.7
RMCD	110.6	143.3	80.2	92.6
JR	97.5	89.6	84.7	79.2
RR	53.8	107.6	62.8	53.8
MS	91.0	116.8	135.6	106.8
MT	82.6	130.0	101.4	99.8
FW	81.9	140.2	85.9	90.6
AW	108.1	70.1	72.8	74.7
MW	63.7	75.2	104.7	81.8
Mean,	91.0	101.9	89.9	88.4
± S.D.	± 32.4	± 35.3	± 31.2	± 36.3

t-tests for paired observations: df = 15

	Flav. drink	Milk	Horlicks
Capsules	t = 1.62 (n.s.)	t = 0.18 (n.s.)	t = 0.65 (n.s.)
Flav. drink	-	-	t = 2.40, p<0.025*
Milk		-	t = 0.33 (n.s.)

\* 1-tailed level of significance

TABLE 5.5. COMPARISON OF FOUR BEDTIME TREATMENTS: WHOLE NIGHT MEASURES  
Mean total min stage 2 sleep accumulated during the whole night.  
Each value for each of 16 subjects is the mean of 5 consecutive nights.

Subjects	Mean total min of stage 2			
	Capsules	Flavoured drink	Milk	Horlicks
KB	207.7	224.2	215.3	210.5
MC	234.7	227.4	199.6	215.0
FC	270.1	271.2	263.7	275.9
JG	219.8	214.6	222.4	227.4
GH	260.7	263.2	255.1	254.0
WH	194.3	187.2	193.2	217.0
AH	270.8	259.0	284.0	274.3
GJ	272.7	288.6	288.0	282.9
RMCD	213.0	211.0	246.9	257.2
JR	235.4	245.2	262.2	247.2
RR	311.1	275.0	306.1	280.0
MS	293.5	273.9	285.2	300.0
MT	262.2	223.1	252.6	238.7
FW	274.0	269.7	287.1	277.2
AW	238.0	250.0	223.3	256.6
MW	246.8	249.8	203.1	240.7
Mean	250.3	245.8	249.3	253.4
± S.D.	± 32.2	± 28.5	± 35.9	± 27.1

No significant differences between treatments

TABLE 5.6. COMPARISON OF FOUR BEDTIME TREATMENTS: WHOLE NIGHT MEASURES  
Total min of slow wave sleep (stages 3 + 4) accumulated over the whole  
night. Each value for each of 16 subjects is the mean of 5 consecutive  
nights.

Mean total min of slow wave sleep				
Subjects	Capsules	Flavoured drink	Milk	Horlicks
KB	72.6	89.2	71.7	91.2
MC	12.9	17.3	16.7	10.4
FC	76.7	82.3	93.4	85.3
JG	73.1	81.7	93.3	63.5
GH	73.2	68.9	91.3	95.2
WH	64.1	70.5	79.1	52.5
AH	68.5	63.1	66.9	75.7
GJ	78.1	65.8	62.9	69.2
RMcD	100.2	71.5	85.1	80.2
JR	63.0	63.7	41.4	77.9
RR	33.5	44.5	25.4	54.4
MS	40.9	39.8	29.0	41.0
MT	99.9	102.6	105.8	119.0
FW	50.4	16.8	31.3	37.7
AW	64.7	76.4	103.9	74.3
MW	88.6	87.6	85.6	80.5
Mean	66.3	65.1	67.7	69.3
± S.D.	± 23.1	± 24.5	± 29.8	± 25.9

No significant differences between treatments



TABLE 5.7. COMPARISON OF FOUR BEDTIME TREATMENTS: WHOLE NIGHT MEASURES

Mean total min of stage REM sleep accumulated over the whole night.

Each value for each of 16 subjects is the mean of 5 consecutive nights.

Subjects	Mean total min of REM sleep			
	Capsules	Flavoured drink	Milk	Horlicks
KB	123.9	95.1	106.2	98.1
MC	83.7	72.7	80.1	74.8
FC	80.4	80.0	91.9	73.0
JG	96.1	92.3	100.9	95.2
GH	97.2	105.4	97.9	106.2
WH	94.8	100.9	111.9	94.5
AH	85.3	99.7	93.4	87.9
GJ	103.4	104.2	96.9	105.6
RMcD	82.7	69.2	97.1	80.4
JR	76.1	70.8	91.2	75.8
RR	109.1	77.9	106.4	110.0
MS	86.0	82.6	57.2	65.8
MT	50.5	49.6	48.9	48.9
FW	96.2	74.9	81.3	93.8
AW	118.9	114.8	107.5	100.4
MW	96.9	85.4	74.4	72.6
Mean	92.6	86.0	90.2	86.4
± S.D.	± 17.5	± 17.0	± 17.9	± 17.0

No significant differences between treatments

TABLE 5.8. COMPARISON OF FOUR BEDTIME TREATMENTS: FIRST 6 h TOTALS  
Mean min of intervening wakefulness occurring in the accumulation of  
the first 6 h of sleep. Each value for each of 16 subjects is the  
mean of 5 consecutive nights.

Mean min intervening wake in 1st 6 h sleep				
Subjects	Capsules	Flavoured drink	Milk	Horlicks
MW	11.7	7.1	71.1	17.2
AW	31.4	8.3	16.2	19.2
AH	17.7	21.5	9.3	11.2
KB	25.3	11.1	33.4	27.9
JR	45.3	24.1	29.0	29.3
JG	48.2	38.1	13.6	2.8
GH	22.3	36.2	36.2	8.3
WH	20.0	24.5	19.2	15.7
MT	23.2	73.5	30.9	29.5
RMCD	56.5	101.3	30.6	23.1
FC	11.9	6.4	6.5	8.4
MC	20.7	32.2	64.7	74.4
GJ	0.0	3.2	3.0	0.0
MS	0.0	1.8	49.2	0.6
FW	17.9	78.1	17.6	26.5
RR	3.2	48.2	9.6	2.4
Mean	22.2	32.2	27.5	18.5
± S.D.	± 16.5	± 29.7	± 20.1	± 18.2

t-tests for paired observations, between planned comparisons: df = 15

	Flav. drink	Milk	Horlicks
Capsules	t = 1.53 (n.s.)	t = 0.80 (n.s.)	t = 0.70 (n.s.)
Flav. drink	-	-	t = 1.77, p<0.05*
Milk		-	t = 1.92, p<0.05*

\* 1-tailed level of significance

TABLE 5.9. COMPARISON OF FOUR BEDTIME TREATMENTS: FIRST 6h TOTALS

Mean min of intervening wakefulness plus stage 1 occurring in the accumulation of the first 6 h of sleep. Each value for each of 16 subjects is the mean of 5 consecutive nights.

Subjects	Mean min intervening wake + stg 1 in 1st 6 h sleep			
	Capsules	Flavoured drink	Milk	Horlicks
MW	35.1	34.8	103.5	49.0
AW	68.8	42.6	50.1	51.2
AH	52.6	52.8	41.0	38.3
KB	41.3	45.5	63.5	59.8
JR	79.5	63.6	69.6	60.4
JG	78.7	71.8	57.2	36.9
GH	43.1	57.6	59.8	29.4
WH	85.1	84.3	75.2	75.8
MT	42.8	109.5	61.4	62.0
RMCD	88.6	135.2	61.1	55.2
FC	43.5	38.0	28.9	37.7
MC	88.1	100.5	132.5	143.9
GJ	22.6	23.1	34.5	21.1
MS	23.0	23.3	81.5	21.7
FW	54.6	138.4	57.0	66.4
RR	34.2	92.3	48.2	36.3
Mean	55.1	69.6	64.1	52.8
± S.D.	± 23.1	± 37.1	± 25.7	± 29.1

t-tests for paired observations between planned comparisons: df=15.

	Flav. drink	Milk	Horlicks
Capsules	t=1.83 (n.s.)	t=1.25 (n.s.)	t=0.39 (n.s.)
Flav. drink	-	-	t=1.98, p<0.05* (1-tailed)
Milk	-	-	t=2.14, p<0.025* (1-tailed)



TABLE 5.10. COMPARISON OF FOUR BEDTIME TREATMENTS :  
FIRST 3h AND SECOND 3h TOTALS.

Mean min of stages 3 + 4 accumulated in the first 3h and the first 6h of sleep. Each value for each of 16 subjects is the mean of 5 consecutive nights.

Subjects	Mean min stages 3+4.							
	Capsules		Flavoured drink		Milk		Horlicks	
	1st 3h	1st 6h	1st 3h	1st 6h	1st 3h	1st 6h	1st 3h	1st 6h
MW	72.9	83.9	67.7	87.4	74.2	91.7	61.4	78.6
AW	40.8	59.6	39.7	62.9	60.6	90.1	52.3	69.9
AH	35.2	67.8	45.0	64.8	31.2	60.8	54.1	63.4
KB	65.5	72.6	69.1	83.7	59.7	68.9	65.3	91.2
JR	47.3	61.0	46.8	62.2	37.6	41.3	49.4	70.7
JG	45.5	63.4	50.4	77.1	45.2	79.7	41.2	59.3
GH	57.8	69.5	47.1	63.1	65.2	88.3	51.7	85.4
WH	53.6	65.0	48.5	68.0	69.3	79.1	38.4	45.4
MT	68.6	93.2	73.9	95.9	68.5	96.0	89.0	109.9
RMCD	66.3	96.1	47.3	76.3	59.9	80.2	54.6	77.7
FC	49.3	70.8	45.1	72.0	67.0	87.6	55.2	75.4
MC	5.7	10.2	6.8	18.5	6.7	18.9	7.6	10.4
GJ	50.6	71.5	47.1	62.2	40.7	59.2	44.5	65.0
MS	26.8	41.1	27.6	38.1	24.7	30.9	32.0	41.0
FW	31.3	48.3	10.1	13.3	17.1	31.3	25.6	35.7
RR	20.3	31.6	17.0	23.1	18.2	23.5	36.6	43.0
Mean	46.1	62.9	43.1	60.5	46.6	64.2	47.4	63.9
±S.D.	±18.8	±22.0	±19.5	±24.7	±21.9	±26.8	±18.2	±24.4

No significant differences between treatments.

TABLE 5.11. COMPARISON OF FOUR BEDTIME TREATMENTS: FIRST 6 h TOTALS

Mean min of stage REM sleep accumulated in the first 6 h of sleep.

Each value for each of 16 subjects is the mean of 5 consecutive nights.

Subjects	Mean min REM in 1st 6 h sleep			
	Capsules	Flavoured drink	Milk	Horlicks
MW	56.5	52.2	57.8	48.1
AW	62.4	71.6	69.8	60.1
AH	50.8	56.6	52.4	49.0
KB	73.7	53.6	74.7	57.5
JR	56.1	49.0	62.3	57.3
JG	84.4	63.4	70.5	70.2
GH	66.0	68.6	56.5	66.3
WH	63.3	69.6	65.5	66.4
MT	29.4	37.8	32.5	29.8
RMCD	55.1	58.3	63.3	52.6
FC	53.6	50.7	57.3	46.6
MC	68.3	58.6	68.0	65.3
GJ	65.0	65.9	61.6	66.9
MS	52.0	62.5	47.0	43.0
FW	59.8	49.0	53.7	66.1
RR	71.1	61.0	75.4	70.8
Mean	60.5	58.0	60.5	57.3
± S.D.	± 12.2	± 9.1	± 11.0	± 11.6

No significant differences between treatments

TABLE 5.12. COMPARISON OF FOUR BEDTIME TREATMENTS: FIRST 6 h TOTALS

Mean number of transitions of sleep stage to wakefulness plus transitions to stage 1, in the accumulation of the first 6 h of sleep. Each value for each of 16 subjects is the mean of 5 consecutive nights.

Mean number of shifts to awake + stg 1 in 1st 6 h of sleep				
Subjects	Capsules	Flavoured drink	Milk	Horlicks
MW	24	22	29	27
AW	34	29	27	32
AH	34	30	27	27
KB	16	30	24	17
JR	22	22	21	26
JG	37	39	47	47
GH	20	18	20	17
WH	48	52	40	55
MT	22	20	23	24
RMCD	23	23	23	28
FC	34	35	23	32
MC	55	62	52	54
GJ	20	18	28	21
MS	22	29	35	26
FW	21	27	19	24
RR	19	25	23	20
Mean	28	30	29	30
± S.D.	± 11	± 12	± 10	± 12

No significant differences between treatments



TABLE 5.13. COMPARISON OF FOUR BEDTIME TREATMENTS: FIRST 3h AND SECOND 3h TOTALS.

Mean min of intervening wakefulness occurring in the accumulation of the first 3h and the second 3h of sleep. Each value for each of 16 subjects is the mean of 5 consecutive nights.

Subjects	Mean min intervening wakefulness							
	Capsules		Flavoured drink		Milk		Horlicks	
	1st 3h	2nd 3h	1st 3h	2nd 3h	1st 3h	2nd 3h	1st 3h	2nd 3h
MW	2.3	9.3	5.3	1.9	35.3	35.8	6.8	7.5
AW	27.0	4.4	1.5	6.8	11.1	5.0	16.3	2.7
AH	14.6	3.0	21.1	0.4	9.3	0.0	9.1	2.0
KB	0.8	24.5	4.7	6.4	11.1	22.3	2.1	25.8
JR	34.2	11.1	7.0	17.2	20.0	9.0	10.5	18.9
JG	0.0	48.2	0.8	37.3	1.6	12.0	0.9	1.9
GH	18.6	3.7	29.1	7.1	35.6	0.7	2.8	5.5
WH	5.9	14.1	7.3	17.2	4.1	15.1	3.4	12.2
MT	1.6	21.6	37.1	36.3	0.4	30.5	0.9	28.6
RMCD	31.3	25.2	56.2	45.0	25.4	5.2	3.6	19.5
FC	6.3	5.6	0.5	5.9	2.3	4.2	4.8	3.6
MC	9.9	10.8	10.0	22.1	21.2	43.4	17.7	56.5
GJ	0.0	0.0	0.0	3.2	1.8	1.1	0.0	0.0
MS	0.0	0.0	1.8	0.0	0.9	48.3	0.0	0.6
FW	14.2	3.7	46.9	31.2	13.5	4.1	25.2	1.3
RR	2.6	0.6	38.7	9.5	3.0	6.6	1.8	0.7
Mean min	10.6	11.6	16.8	15.5	12.3	15.2	6.6	11.7
$\pm$ S.D.	$\pm 11.7$	$\pm 12.9$	$\pm 18.8$	$\pm 14.7$	$\pm 12.0$	$\pm 15.9$	$\pm 7.4$	$\pm 15.3$

t = tests for paired observations

(see Table 5.14).

TABLE 5.14. STATISTICAL ANALYSIS OF DATA IN TABLE 5.13

Mean min of intervening wakefulness occurring in the accumulation of the first 3 h and the second 3 h of sleep

(a) First 3 h of sleep

Mean min intervening wakefulness

	Capsules	Flav. drink	Milk	Horlicks
Mean min $\pm$ S.D.	10.6 $\pm$ 11.7	16.8 $\pm$ 18.8	12.3 $\pm$ 12.0	6.6 $\pm$ 7.4

t-tests for paired observations: df = 15 (2-tailed)

	Flav. drink	Milk	Horlicks
Capsules	t = 1.31 (n.s.)	t = 0.57 (n.s.)	t = 1.49 (n.s.)
Flav. drink	-	-	t = 2.13p = 0.05*
Milk		-	t = 1.87 (n.s.)

\*not significant

(b) Second 3 h of sleep

Mean min intervening wakefulness

	Capsules	Flav. Drink	Milk	Horlicks
Mean min $\pm$ S.D.	11.6 $\pm$ 12.9	15.5 $\pm$ 14.7	15.2 $\pm$ 15.9	11.7 $\pm$ 15.3

t-tests for paired observations: df = 15 (2-tailed)

	Flav. drink	Milk	Horlicks
Capsules	t = 1.37 (n.s.)	t = 0.73 (n.s.)	t = 0.02 (n.s.)
Flav. drink			t = 0.88 (n.s.)
Milk			t = 1.27 (n.s.)



TABLE 5.15. COMPARISON OF FOUR BEDTIME TREATMENTS:

FIRST 3h AND SECOND 3h TOTALS.

Mean min of stage REM sleep accumulated in the first 3h and the second 3h of sleep. Each value for each of 16 subjects is the mean of 5 consecutive nights.

Subjects	Mean min stage REM							
	Capsules		Flavoured drink		Milk		Horlicks	
	1st 3h	2nd 3h	1st 3h	2nd 3h	1st 3h	2nd 3h	1st 3h	2nd 3h
MW	18.6	37.9	18.4	33.8	19.5	38.1	16.9	31.2
AW	18.7	43.8	28.8	42.8	21.9	48.0	21.7	38.5
AH	20.5	30.3	23.1	33.5	26.5	26.0	19.4	29.6
KB	23.1	50.6	19.0	34.6	21.3	53.4	24.3	33.2
JR	14.9	41.2	18.7	30.3	16.8	45.5	18.3	38.9
JG	30.7	53.7	25.2	38.2	33.6	37.0	29.6	40.6
GH	18.9	47.1	22.5	46.1	21.2	35.3	29.3	37.0
WH	24.1	39.2	28.6	41.0	19.7	45.7	27.2	39.2
MT	4.7	24.6	8.3	29.5	10.8	21.7	8.3	21.5
RMCD	26.3	28.8	25.6	32.7	13.4	50.0	12.4	40.2
FC	17.5	36.1	22.6	28.1	24.7	32.7	14.6	32.0
MC	25.9	42.4	28.2	30.4	28.4	39.5	26.4	38.8
GJ	29.4	35.6	17.3	48.6	24.7	36.3	23.3	43.6
MS	15.3	36.7	21.5	41.0	8.6	38.4	9.8	33.2
FW	23.5	36.3	18.8	30.2	12.0	41.7	14.1	52.0
RR	22.1	49.0	20.9	40.1	17.3	58.1	30.4	40.4
Mean	20.9	39.6	21.7	36.3	20.0	40.5	20.4	36.9
	$\pm 6.3$	$\pm 8.1$	$\pm 5.2$	$\pm 6.3$	$\pm 6.8$	$\pm 9.6$	$\pm 7.2$	$\pm 6.8$

No significant differences between treatments.



TABLE 5.16. COMPARISON OF FOUR BEDTIME TREATMENTS: SUBJECTIVE RATINGS  
 Mean subjective rating from each of 16 subjects for sleep quality during  
 (a) The 15 nights at home prior to attending the sleep laboratory  
 (b) The 6 nights that subjects attended the sleep laboratory

Subjects	Mean subjective sleep quality in mm <sup>*</sup>							
	Capsules		Flavoured drink		Milk		Horlicks	
	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)
AW	57	45	56	45	50	45	50	46
MW	53	45	50	49	55	45	52	47
AH	72	77	76	76	63	71	66	69
KB	50	43	50	43	48	40	46	44
JR	62	49	53	54	61	65	55	49
JG	51	47	53	41	54	41	56	53
GH	60	54	57	59	56	52	53	48
WH	56	42	56	45	55	53	51	47
MT	49	45	49	39	52	41	50	42
RMCD	53	61	53	49	55	50	53	58
FC	50	51	50	59	49	56	55	47
MC	48	46	49	49	47	46	51	46
GJ	50	43	52	40	52	47	51	46
FW	69	60	66	56	67	66	68	58
RR	53	54	53	57	52	49	48	51
MS	71	85	61	65	52	64	64	58
Mean	57	53	55	52	54	52	54	51
± S.D.	± 8	± 13	± 7	± 10	± 6	± 10	± 6	± 7

\*Omm = "Worst possible" sleep quality

100 mm = "Best possible" sleep quality

No significant differences between treatments

TABLE 5.17. COMPARISON OF FOUR BEDTIME TREATMENTS: SUBJECTIVE RATINGS

Mean subjective rating from each of 16 subjects for morning vigilance during: (a) The 15 days at home prior to attending the sleep laboratory  
(b) The 6 days that subjects attended the sleep laboratory

Subjects	Mean subjective morning vigilance in mm <sup>*</sup>							
	Capsules		Flavoured drink		Milk		Horlicks	
	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)
AW	48	49	43	51	44	47	47	46
MW	49	52	54	51	45	57	46	56
AH	56	56	59	47	54	50	53	55
KB	51	53	50	56	50	55	49	53
JR	49	34	48	38	43	42	49	39
JG	52	51	56	49	62	58	51	48
GH	54	49	54	52	52	50	53	53
WH	49	39	45	43	45	44	60	53
MT	58	62	56	55	56	52	53	54
RMCD	49	53	49	49	39	44	46	47
FC	48	49	45	49	48	42	42	35
MC	48	47	49	44	46	47	50	47
GJ	46	47	46	48	48	48	54	47
FW	42	34	39	39	41	49	44	49
RR	49	50	49	51	49	51	51	46
MS	28	24	30	26	47	46	43	37
Mean	49	47	48	47	48	49	49	48
± S.D.	± 7	± 10	± 7	± 8	± 6	± 5	± 5	± 6

\*Where 0 mm = "Marvelously alert and energetic"

Where 100 mm = "Awfully sleepy and lack-lustre"

No significant differences between treatments

TABLE 5.18. COMPARISON OF FOUR BEDTIME TREATMENTS: SUBJECTIVE RATINGS

Mean subjective rating from each of 16 subjects for daytime anxiety

during (a) The 15 days at home prior to attending the sleep laboratory

(b) The 6 days that subjects attended the sleep laboratory at night

Subjects	Mean subjective anxiety in mm *							
	Capsules		Flavoured drink		Milk		Horlicks	
	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)
AW	47	52	51	53	48	48	49	49
MW	51	52	53	54	60	59	51	56
AH	62	55	52	55	59	66	49	62
KB	51	50	48	50	49	47	48	49
JR	45	44	48	50	52	57	49	59
JG	48	51	51	45	51	64	48	64
GH	54	49	53	49	53	51	53	50
WH	46	48	42	47	42	47	40	43
MT	41	48	51	50	51	52	50	49
RMCD	46	50	46	47	50	46	47	49
FC	51	51	52	52	50	51	47	48
MC	51	46	50	48	48	47	53	46
GJ	52	49	55	54	56	53	53	51
FW	56	57	54	54	48	53	47	46
RR	50	49	51	49	50	50	48	49
MS	51	52	50	50	48	52	50	49
Mean	50	50	50	50	51	53	49	51
± S.D.	± 5	± 3	± 3	± 3	± 5	± 6	± 3	± 6

\*Where 0 mm = "Terrible agitation"

Where 100 mm = "Imperturbable tranquility"

No significant differences between treatments



TABLE 5.19. COMPARISON OF FOUR BEDTIME TREATMENTS.

The 16 subjects' body weights measured 8 times over 13 weeks. On the first and sixth nights of attendance at the sleep laboratory on any one treatment.

Subjects	Body Weight (lb)								Mean body wt. ± S.D.
	First treatment		Second treatment		Third treatment		Fourth treatment		
	Night		Night		Night		Night		
	1	6	1	6	1	6	1	6	
MS	101.5	102.0	103.0	104.5	104.0	104.5	105.0	105.0	103.69 ± 1.36
JR	119.25	118.0	119.5	117.25	119.0	118.0	119.75	117.75	118.56 ± 0.92
MT	128.75	126.5	127.0	126.5	129.0	128.0	130.0	129.75	128.19 ± 1.41
RMcD	137.0	136.5	136.0	136.0	135.0	135.0	135.0	135.5	135.75 ± 0.76
FW	140.0	139.25	139.0	140.0	141.0	139.0	140.0	140.0	139.78 ± 0.69
RR	141.5	141.75	141.75	143.5	143.0	142.0	142.5	144.0	142.50 ± 0.92
MW	147.75	148.5	147.25	145.75	145.75	145.75	144.25	144.5	146.19 ± 1.52
AH	148.0	147.75	148.75	147.5	146.25	148.5	149.5	149.0	148.16 ± 1.03
WH	147.75	146.5	149.5	147.0	148.0	149.0	150.0	148.5	148.28 ± 1.21
MC	152.5	155.5	155.75	153.5	149.5	150.5	151.5	151.5	152.53 ± 2.26
FC	158.5	157.25	157.5	157.25	157.5	156.5	159.5	158.5	157.81 ± 0.95
GH	161.5	161.5	161.5	160.5	159.25	158.0	158.0	154.5	159.34 ± 2.46
GJ	164.0	164.5	164.5	162.75	164.0	163.5	165.0	163.0	163.91 ± 0.79
AW	171.75	171.0	170.75	170.0	171.75	170.5	170.5	170.5	170.84 ± 0.64
KB	168.75	169.5	172.0	173.0	170.5	174.5	172.25	171.75	171.53 ± 1.88
JG	202.5	202.25	202.75	203.75	201.5	201.0	201.5	199.5	201.84 ± 1.29

# CHAPTER 6

## DIETARY HABITS DETERMINE THE EFFECTS OF BEDTIME EATING ON SLEEP

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## CHAPTER 6

### SUMMARY

Subjects who usually had something to eat before retiring to bed slept better after taking milk or Horlicks at bedtime than after taking an inert capsule, whereas those accustomed to having little or nothing slept better after the capsule.



## INTRODUCTION

In the experiment described in the previous Chapter where four bedtime treatments were compared I commented that the sleep of some subjects appeared to be consistently less broken by wakefulness after they had drunk Horlicks or milk than after taking capsules at bedtime, whereas other subjects consistently slept worse after taking a bedtime food drink than they did after capsules.

I thought that differences in the usual evening dietary habits of the subjects might be the reason as several subjects had spontaneously commented that they felt hungry in the later evening when they took the capsule whereas other subjects said they did not normally take as much food at bedtime and that they preferred the capsule. A post-hoc investigation of each volunteer's dietary habits was undertaken to determine whether a subject's evening dietary pattern was related to his or her changes in sleep in response to bedtime nutrition.

## METHODS

### (a) Assessment of dietary habits.

Subjects were sent, by post, a diet questionnaire (Figure 6.1) and a daily diet diary, an explanatory letter and a stamped return envelope.

All 16 subjects answered the diet questionnaire and in the diet diary gave a detailed report of all they ate on a typical day. They were specifically asked to list as accurately as possible the amounts and the times they usually ate. All six men and eight of the women were married and this, together with the fact that the subjects were of an older age group, made it more likely that their dietary habits would be fairly stable.

Three methods were tried to separate out the subjects into a rank order according to their differing dietary habits in the evening. However, only the third method gave a satisfactory separation of the subjects so that a rank correlation test could be employed.

It was assumed that subjects who normally had a bedtime snack would sleep better in the laboratory after a bedtime food drink than after the capsules, when they had had nothing to eat or drink after 1900h. Conversely it was predicted that subjects who usually ate little or nothing later in the evening would sleep better after the capsules and that their sleep might be impaired by the ingestion of unaccustomed food.

FIGURE 6.1 ASSESSMENT OF DIETARY HABITS

DIET QUESTIONNAIRE

Would you please answer the following questions by ticking the answer which is nearest to your typical day.

- (a) I usually have            (i) large breakfast            ☐
- (ii) medium breakfast        ☐
- (iii) small breakfast        ☐
- (iv) no breakfast            ☐
- (b) I usually have            (i) large lunch               ☐
- (ii) medium lunch            ☐
- (iii) small lunch            ☐
- (iv) no lunch                ☐
- (c) I usually have            (i) large evening meal       ☐
- (ii) medium evening meal    ☐
- (iii) small evening meal    ☐
- (iv) no evening meal        ☐
- (d) The time I usually have my evening meal is between:
- (i) 4 - 5 p.m.                ☐
- (ii) 5 - 6 p.m.               ☐
- (iii) 6 - 7 p.m.              ☐
- (iv) 7 - 8 p.m.               ☐
- (v) 8 - 9 p.m.               ☐
- (vi) later                    ☐
- (e) I usually have something to eat or drink later  
    in the evening
- (i) always                    ☐
- (ii) sometimes               ☐
- (iii) rarely                   ☐
- (iv) never                    ☐
- (f) If I have something to eat or drink later in  
    the evening (please describe and please specify  
    any alcohol taken) I usually have:
- .....
- (g) Do your answers above differ from those you would  
    have given at the time just before you took part  
    in the 'nutrition and sleep' experiment?
- (i) yes                       ☐



(i) Unsuccessful ranking methods I and II

A colleague was asked to assign ranks to the subjects' answers to the Diet Questionnaire. This first attempt to rank subjects according to their evening eating habits only employed their answers to questions (c), (d) and (e) of the Diet Questionnaire (Figure 6.1). All subjects answered "no" to question (g). Their answers to these questions were given numbered scores, i.e.

question (c) I usually have (i) large evening meal ...  
(ii) medium evening meal...  
(iii) small evening meal ...  
(iv) no evening meal .....

A tick against (i) scores 1 point (ii) 2 points  
(iii) 3 points, (iv) 4 points, on the assumption that the larger evening meal (in relative terms) the less likely the person would need a bedtime snack. The timing of the evening meal was also considered to have a bearing on whether a subject would benefit from a bedtime food drink and thus the earlier the evening meal was eaten the higher the score, i.e.

question (d) The time I usually have my evening meal

is between	(i)	4-5 p.m.	}	3 points
	(ii)	5-6 p.m.		
	(iii)	6-7 p.m.	}	2 points
	(iv)	7-8 p.m.		
	(v)	8-9 p.m.	}	1 point
	(vi)	later		

The/

The frequency of having a bedtime snack was investigated by question (e).

I usually have something to eat or drink later in the evening -

	Scoring
(i) always	4 points
(ii) sometimes	3 points
(iii) rarely	2 points
(iv) never	1 point

On this scoring system it was predicted that the subjects with the higher scores would sleep better after bedtime food drinks than after the acaioric capsules whereas subjects with the lower scores would not. This method failed to separate subjects adequately into a rank order and it did not take into account the size of the bedtime snack.

The second method of ranking included some weighting for the contribution of the bedtime eating habits of subjects. The answers to questions (c), (d) and (e), in the Diet Questionnaire were scored as described above but in addition the size of the evening snack, described in answer to question (f), was rated on a three-point scale and added to the score obtained above if they answered always or sometimes to question (e). Subjects who had only a cup of tea or coffee had nothing added to their score, those who had a small snack such as a biscuit had 1 point added, and a more substantial snack was given an extra score of 2 points.

This/

This method was better in separating subjects into a rank order as it included a rating of the size of the bedtime snack and indicated that an even better separation would be achieved if the evening energy intakes of subjects were analysed.

(ii) Method III used to assess dietary habits

The third method was the one actually used to rank subjects and involved an assessment of the calorie intake of subjects on a typical day and thus was a more sensitive measure of the usual bedtime intake of each subject.

McCance and Widdowson's (1960) book of the composition of common foodstuffs and a booklet of calorie values of branded foods (Slimming Magazine, 1974) were used to estimate the energy intake of subjects. The average calorie intake through the day was estimated first by myself and then independently by a dietician not involved in this study. Many of the subjects listed a range of typical lunches, evening meals and, if they had one, bedtime snacks. The method I used to estimate their calorie intake through the day was to score all the alternative meal menus listed by a subject and then calculate the maximum and minimum calorie intake/



intake for the whole day and for both the evening meal and the bedtime snack. Thereafter the means, of the maximum and minimum calorie intakes were calculated.

The independent dietician used a different method to assess calorie intake. She selected one set of the alternatives listed for each meal and estimated the energy content taking into account the age, sex, weight and occupation of each subject.

(b) 'Predicted' order of benefit from bedtime nutrition: Ranking subjects according to their dietary habits.

I devised the following method of assessment of dietary habit in order to rank subjects according to the relative amount of food they ate in the later evening. All the subjects took their evening meal sometime between 1700h and 2000h and none took their bedtime snack before 2130h (ascertained from answers to the diet questionnaire).

A rating of "predicted" benefit from later evening nourishment was made by the ratio below, which was designed to give a measure of the relative contribution of bedtime eating to the total energy intake after 1700h.

$$\frac{\text{calorie intake after 2100}}{\text{total calorie intake after 1700h}} \times 100 = N\%$$

Subjects were then ranked, according to their N% score/

score in order of "predicted" benefit from food eaten later in the evening on the assumption that those who normally took relatively more calories after 2100h would sleep better after a nourishing bedtime drink than after an acaloric capsule. The subject who was predicted to sleep best after bedtime food compared with after capsules was ranked number one. If two subjects tied on their N% score, then the size of their evening meal (food between 1700h and 2100h) was taken into account by converting the calorie content of their evening meal into a percentage of their daily intake:

$$\frac{\text{calorie intake between (1700h and 2100h)}}{\text{total daily calorie intake}} \times 100 = \text{EM\%}.$$

It was predicted that the lower the EM% score the more likely that food taken later in the evening would have a beneficial effect on sleep. The EM% score was used to rank the two subjects who had an N% score of 0%. Subjects covered a wide range of N% (0% to 41%). The dietician's ordering of subjects according to her estimates of N% was used for all calculations.

(c) Ranking subjects according to changes in sleep in response to bedtime nutrition.

A measure of benefit (i.e. improvement in sleep for each of the three bedtime drinks compared with capsules) was calculated for each subject by, for example, subtracting his/her mean total time asleep recorded while taking one of the bedtime drinks from the mean total time asleep when he/she was taking capsules. This procedure was repeated for all the measures of sleep i.e. total sleep time, total wakefulness recorded after sleep onset and until the recording finished, the total min of intervening wakefulness in the first 3h, second 3h and first 6h of accumulated sleep and the total min of intervening wakefulness plus total min of stage 1 sleep in the first 6h of accumulated sleep. The differences were then ranked in descending order for the "measured" benefit derived from bedtime food, i.e. for each food drink, the subject who slept best after the bedtime food drink in comparison with his sleep after the capsule was rated 1 and the subject who slept worst after the food drink compared with that after the capsule was ranked 16.



(d) Statistics

Spearman's rank correlation test (Siegel, 1956) was used to compare the "predicted" order of benefit to sleep from bedtime food (N%'s ranked 1 to 16) with the "measured" rank orders of the differences between the results on capsules and those after each of the three bedtime food drinks.

## RESULTS

(a) Ranking the 16 subjects into a 'predicted' order of benefit from bedtime nutrition.

(i) Methods I and II

Table 6.1 shows the ratings given to the different subjects using Method I and Method II. These two methods were discarded as they gave insufficient separation to rank subjects in order 1 to 16.

(ii) Method III

Table 6.2 shows the author's predicted order 1 to 16 of benefit from food at bedtime using the method described earlier to calculate N% and EM%. N% scores (the usual intake of calories after 2100h as a percentage of the individual's intake after 1700h) ranged from 0% to 41.14%. Only the two subjects with N% = 0% had to have their EM% taken into account. EM% (the usual calorie intake at the evening meal as the percentage of the total intake of calories through the day) varied from 28% to 56%.

Table 6.3 shows the independent dietician's rank order 1 to 16 of predicted benefit from bedtime nourishment using her values of N% and EM% for each subject. Her estimates of N% ranged from 0% to 40.63% and only two subjects tied on their N%, those with N% = 0%, and had their EM% considered. EM% ranged from 26% to 50%.

The ranking of subjects into the predicted order of benefit from food eaten at bedtime calculated by me and by the dietician were very similar (Table 6.4) and the correlation between our rank orders was  $r_s = 0.982$ ,  $p < 0.00002$ , 1-tailed. However, the dietician's rank order was used in all the calculations.

(b) Correlations between 'predicted' and 'measured' orders of benefit from bedtime food.

The predicted order was of the subjects ranked in descending order 1 to 16 according to their N% scores such that the subject ranked 1 was predicted to gain the most benefit to his sleep from food eaten at bedtime compared with his sleep when taking capsules at bedtime. Conversely the subject ranked 16 was predicted to sleep better after capsules than after a food drink at bedtime. The results are presented for each measure of sleep and wakefulness as the difference in min between the mean over the five nights on capsules and the mean over the five nights on each of the food drinks and these differences were ranked 1 to 16 in descending order of benefit from bedtime nourishment.

(i) Whole night measures.

The rank orders of measured benefit to sleep from milk and Horlicks were both significantly correlated with the order predicted from the subjects' usual eating pattern/



pattern. This was true for the mean total time that subjects slept (Table 6.5) and for the total time that subjects were awake between first falling asleep and before lights on in the morning (Table 6.6). The results obtained from flavoured drink gave no significant correlations between the measured and predicted orders of benefit from bedtime nourishment (Tables 6.5; 6.6).

The rank orders calculated for the benefit of milk and of Horlicks were significantly correlated with each other, e.g. the rank correlation between the orders of differences in total sleep time for milk and Horlicks was  $r_s = 0.82$ ,  $p < 0.001$  (Table 6.5) and similarly for total wakefulness after first falling asleep the correlation between the rank orders on milk and Horlicks was  $r_s = 0.66$ ,  $p < 0.01$  (Table 6.6).

(ii) Brokenness of sleep in the first 6h, first 3h and second 3h of sleep.

Table 6.7 lists the differences and the rank order of the differences between capsules and each of the three bedtime drinks in the mean min of intervening wakefulness occurring in the accumulation of the first 6h of sleep. The rank orders of benefit for both Horlicks and milk were positively correlated with the order predicted from subjects' N% scores:  $r_s = 0.64$ ,  $p < 0.01$ ;  $r_s = 0.53$ ,  $p < 0.05$  respectively (Figures 6.2; 6.3). The/

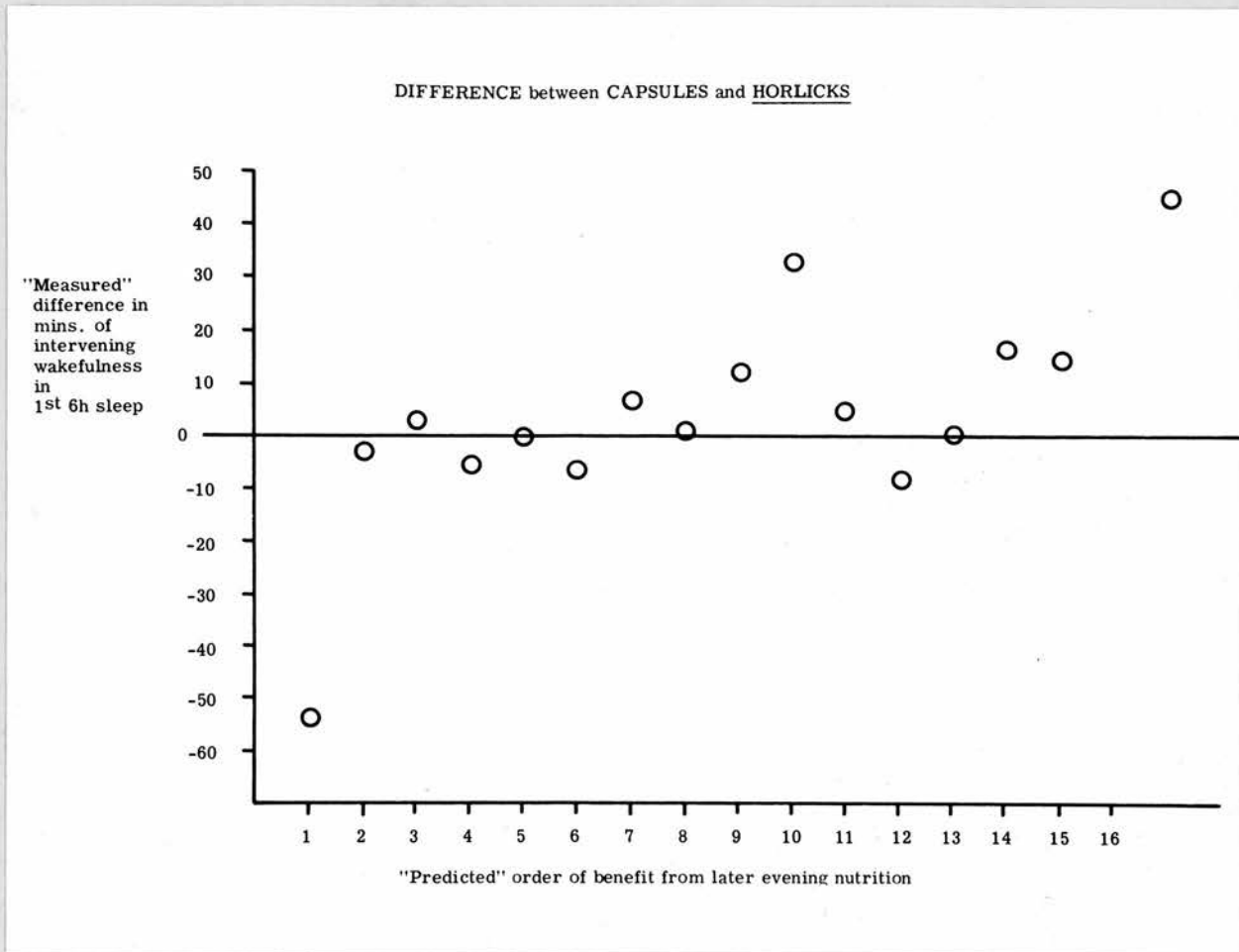


FIGURE 6.2 The measured difference in min of intervening wakefulness accumulated in the first 6h of sleep between the mean of the 5 nights recorded while on capsules and mean of the 5 nights while taking Horlicks, for each of the 16 subjects.

The horizontal axis is the 16 subjects ranked in ascending order of predicted benefit from bedtime food (i.e. 1 = least and 16 = most benefit)

Statistical analysis in Table 6.7.

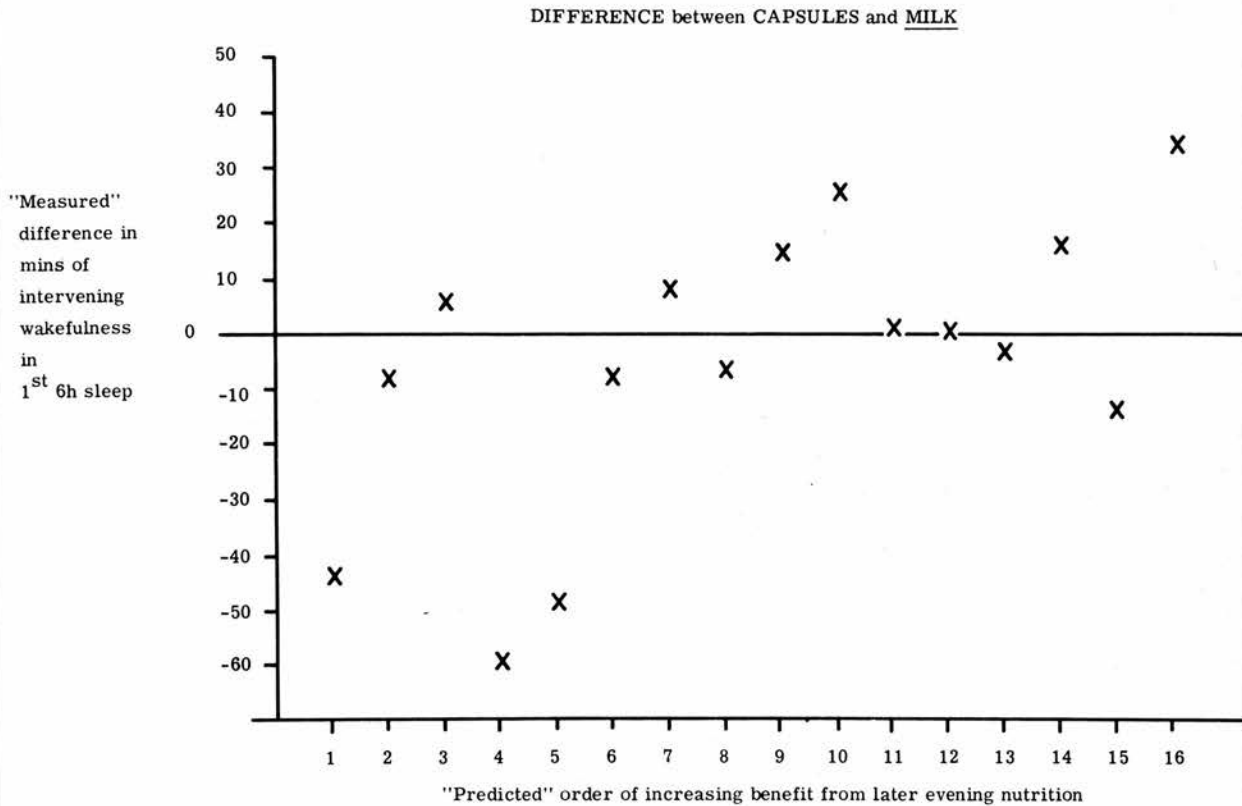


FIGURE 6.3 The measured difference in min of intervening wakefulness accumulated in the first 6h of sleep between the mean of the 5 nights recorded while on capsules and the mean of the 5 nights while taking milk for each of 16 subjects.

The horizontal axis is the 16 subjects ranked in ascending order of predicted benefit from bedtime food.

Statistical analysis in Table 6.7.



The rank order for milk was positively correlated with the rank order for Horlicks  $r_s = 0.74$ ,  $p < 0.002$ . The rank order for flavoured drink was not correlated with the predicted order of benefit (Figure 6.4).

If the night was treated as the first 3h (Table 6.8) and the second 3h (Table 6.9) the only significant correlation with the predicted order was found for the benefit of milk in the second 3h of sleep.

The rank orders of benefit to sleep, measured as a reduction of both intervening wakefulness and stage 1 in the first 6h of sleep from Horlicks or milk at bedtime are shown in Table 6.10. Horlicks and milk both gave positive correlations between their measured order and their predicted order of benefit:  $r_s = 0.68$ ,  $p < 0.01$ ;  $r_s = 0.50$ ,  $p < 0.05$  respectively (Figures 6.5; 6.6). Again, the rank order for flavoured drink was not significantly correlated with the ranked N% scores (Figure 6.7). The rank order of measured benefit for milk was significantly correlated with that for Horlicks  $r_s = 0.83$ ,  $p < 0.001$ .

(iii) No correlation with treatment order

In the original experimental design the order of administering the four bedtime treatments was balanced over the 16 subjects, but in the method of investigating dietary habit described above this exact balancing is diminished/

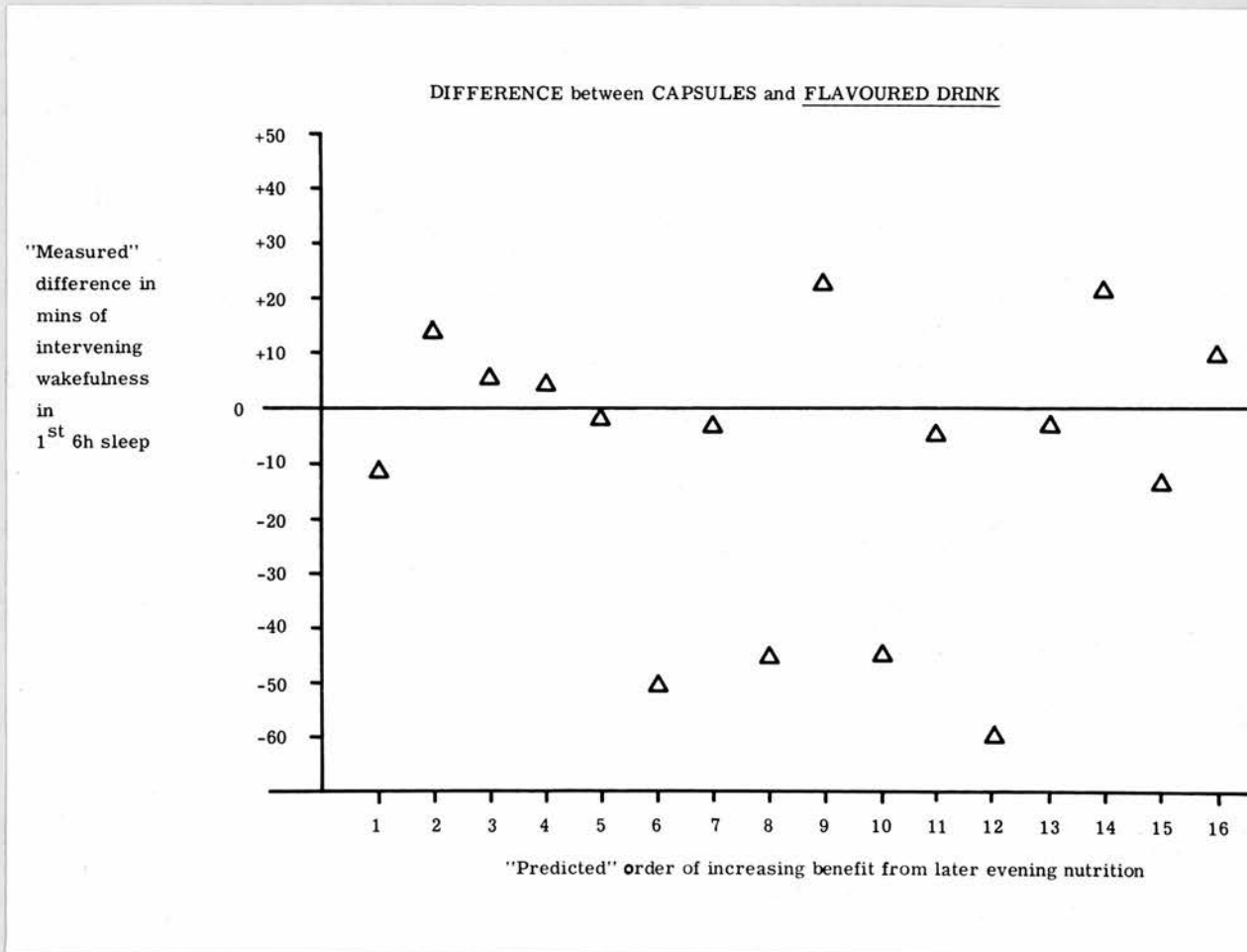


FIGURE 6.4 The measured difference in min of intervening wakefulness accumulated in the first 6h of sleep between the mean of the 5 nights recorded while on capsules and the mean of the 5 nights while taking flavoured drink, for each of 16 subjects.

The horizontal axis is the 16 subjects ranked in ascending order of predicted benefit from bedtime food.

Statistical analysis in Table 6.7.

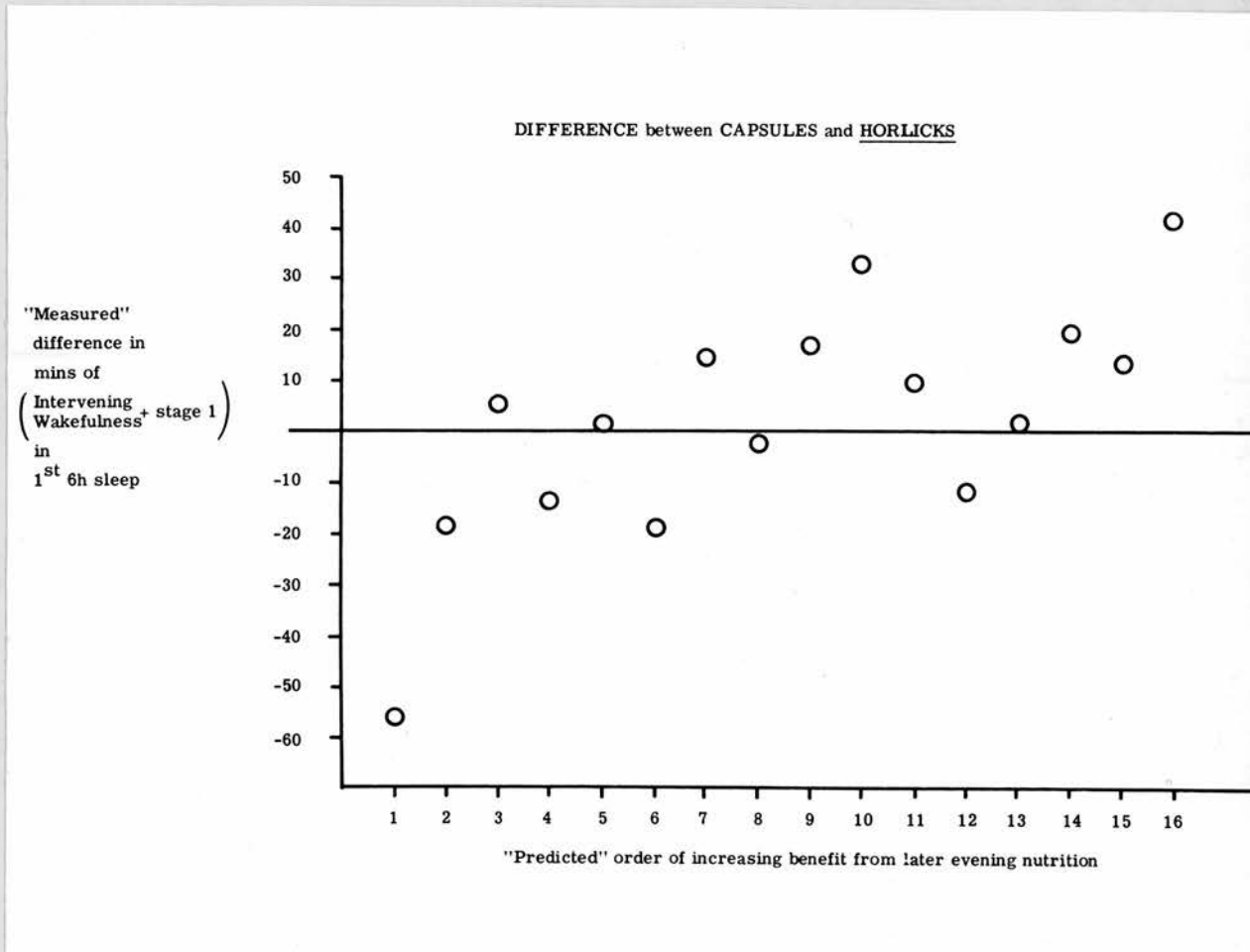


FIGURE 6.5 The measured difference in min of intervening wakefulness combined with min of stage 1 accumulated in the first 6h of sleep between the mean of the 5 nights recorded while on capsules and the mean of the 5 nights while taking Horlicks, for each of 16 subjects.

The horizontal axis is the 16 subjects ranked in ascending order of predicted benefit from bedtime food.

Statistical analysis in Table 6.10.



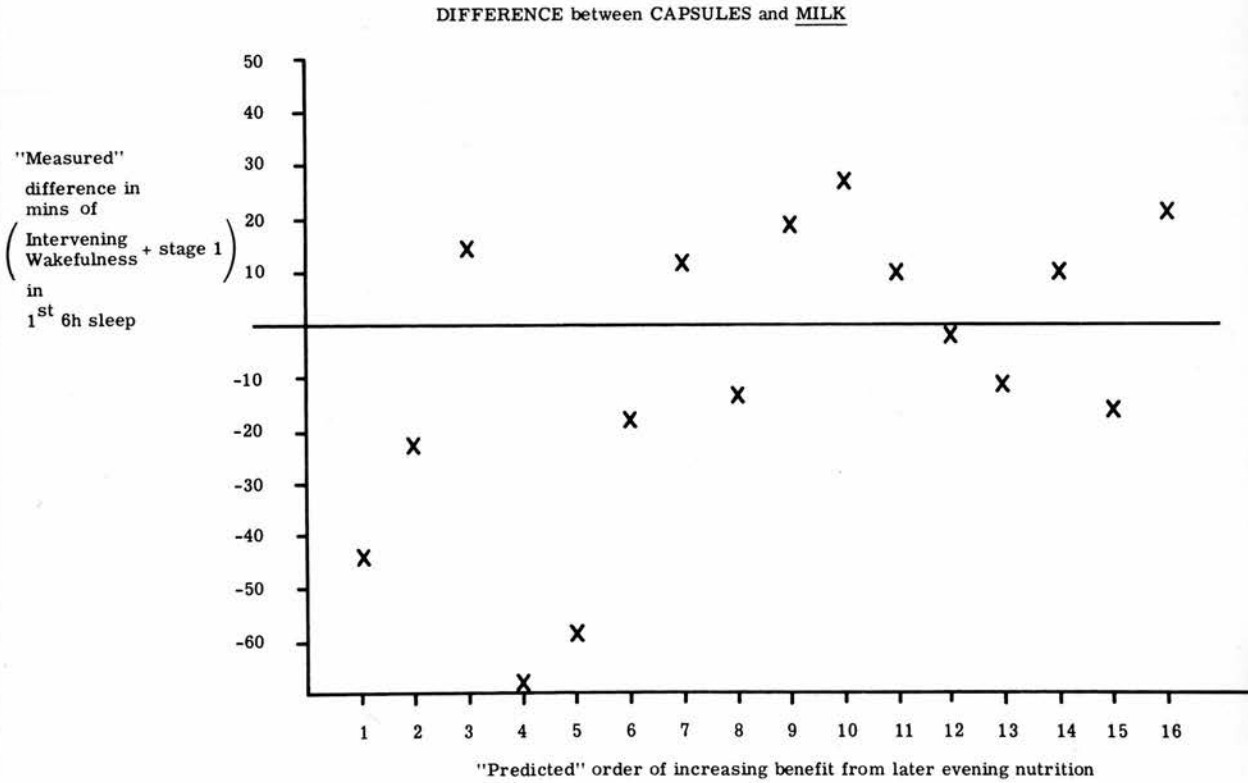


FIGURE 6.6 The measured difference in min of intervening wakefulness combined with the min of stage 1 accumulated in the first 6h of sleep between the mean of the 5 nights recorded while on capsules and the mean of the 5 nights while taking milk, for each of 16 subjects.

The horizontal axis is the 16 subjects ranked in ascending order of predicted benefit from bedtime food.

Statistical analysis in Table 6.10.

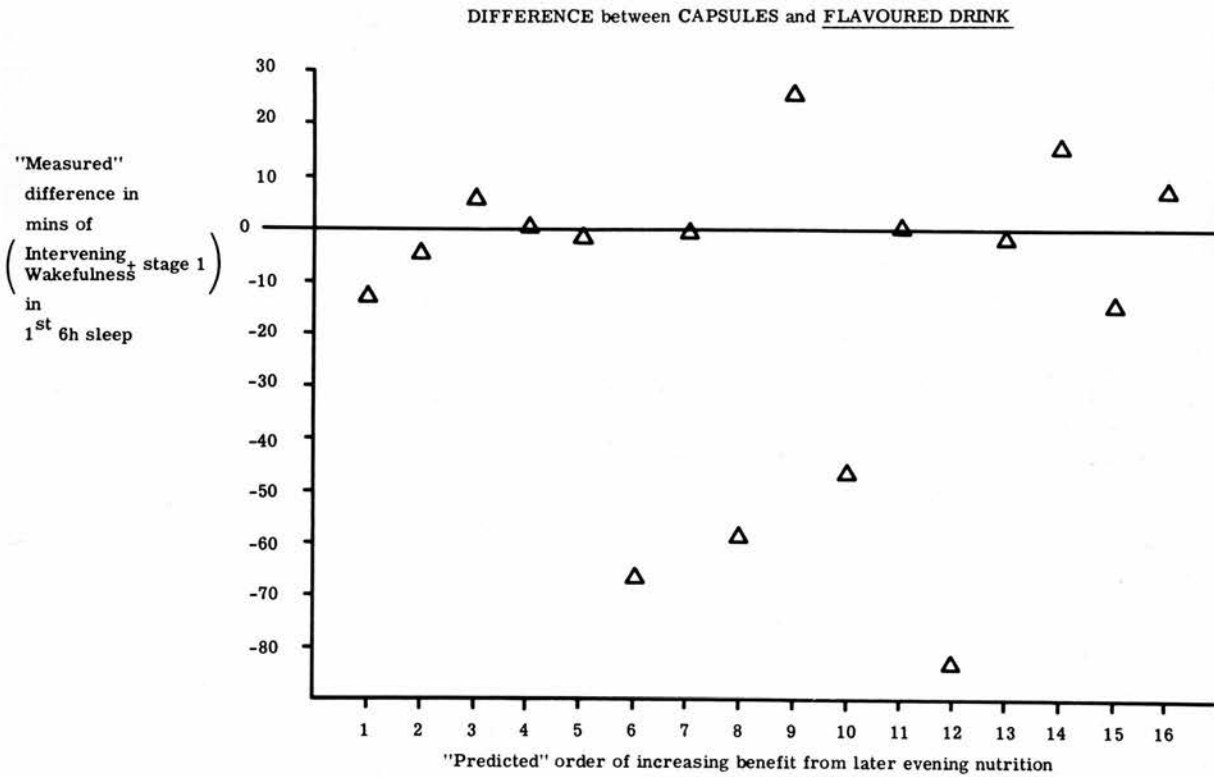


FIGURE 6.7 The measured difference in min intervening wakefulness combined with the min of stage 1 accumulated in the first 6h of sleep between the mean of the 5 nights recorded while on capsules and the mean of the 5 nights while taking flavoured drink, for each of 16 subjects.

The horizontal axis is the 16 subjects ranked in ascending order of predicted benefit from bedtime food.

diminished and so Friedman's analysis of variance by ranks (Siegel, 1956) was employed to test if treatment order had any influence on the total min of wakefulness accumulated between sleep onset and the end of the recording and intervening wakefulness in the first 6h of sleep. Tables 6.11; 6.12 illustrate that there was no significant relationship between treatment order and either of these measures of disturbed sleep.

(iv) Subjective ratings.

The mean subjective ratings of sleep quality over the six consecutive nights when subjects slept at the laboratory at night on capsules was subtracted from the corresponding means for the six nights at the laboratory on each of the three bedtime food drinks. These differences in mm were ranked 1 to 16 in descending order of magnitude. Table 6.13 shows the differences for the mean ratings of sleep quality and the corresponding rank orders. There were no significant correlations between the predicted order of benefit and the measured order of benefit for any of the food drinks.



Three methods were tried to separate the 16 subjects into a rank order of their differing dietary habits. Method III proved the most satisfactory in it's separation of subjects into a rank order and it also took more account of the relative energy value of the usual bedtime food intake of subjects. The size of the bedtime snack obviously had to be in relative terms, for a bedtime snack, of say 300 cal, is a relatively greater bedtime energy intake for someone whose entire evening intake is only 600 cal in comparison with someone who eats 1200 cal over the evening i.e. 50% compared to 25% respectively of evening intake eaten at bedtime.

Rank order correlations were used in preference to product moment correlations because although I did have actual values of N% scores these were based on only one typical day's dietary intake. Subjective recall of the amount eaten is known often to be an under or over-estimate. Madden et al. (1976) found that small intakes were frequently over-estimated whereas large intakes were under-estimated and a fair amount of latitude is assumed in the actual number of calories consumed. However, in the calculation of N%  
a/

a ratio of calorie intakes was used and I assumed that subjects would consistently under or over-estimate their intake and so numerator and denominator of the formula calculating N% would be affected in the same direction and so would roughly cancel out. Admittedly, subjects would probably recall their bedtime snack more accurately than their usual evening meal and the percentage error in an under or over-estimation of the evening meal would be greater as its energy content is usually more than the bedtime snack. Energy intake through a typical evening varied widely over the 16 subjects and so even with the disadvantages above, I feel that the Method III used to assess subjects relative energy intake at bedtime was sufficiently accurate to be able to put subjects into a rank order of predicted benefit from bedtime nutrition. Had I wished to use raw values of N% I would have had to ask subjects to keep detailed diet diaries over about seven consecutive days and then take the mean, because studies have shown that about this length of time is required to estimate energy intake accurately (Young et al., 1952). I asked subjects to list a usual day's food and drink consumption and not a particular day, in case it was atypical.

I/

I found that those who usually ate most near bedtime slept well after Horlicks or milk and those who usually ate little or nothing slept worse. And finding all the significant correlations between the predicted and the measured orders of benefit from bedtime food supports the idea that a subjects dietary habits are an important factor in how his or her sleep will change in response to food eaten at bedtime and the close correlations between the rank orders of benefit from milk and from Horlicks give added evidence that this is a genuine relationship. My findings may help to explain the contradictory reports in the literature, where some authors found that bedtime nutrition improved sleep whereas others reported no effect or even a detrimental effect attributable to food eaten near bedtime. I reviewed a selection of these contradictory reports in Chapter 2 and so I will not repeat myself here. Suffice to say that a few of the early reports were based on research of poor quality and lacked any statistical evaluation so that little credence can be placed upon their conclusions. Among the papers that do stand critical appraisal the lack of agreement remains and I feel sure that differences in the dietary habits of the subjects used in these experiments may, in part, be responsible for the contradictory results.

Closer/



Closer inspection of the results reported by Giddings (1934) of nocturnal motility after different bedtime intakes of food, does in fact give an indication of differences between the individuals in their response to bedtime nutrition. To quote "On the nights on which the warm milk was received, it was seen that in 41.7 per cent of the children the activity was diminished; the movement was increased in 8.3 per cent of the children and in 50 per cent of the children there was no change noted" (compared with nothing to eat at bedtime). From which he concludes "The drinking of 6 oz of warm milk at bedtime seems to produce quiet sleep in normal children". He reported that any change in an individual child's sleep owing to bedtime nutrition were consistent over the five nights that motility was recorded on each treatment. His results suggest to me that the children varied in their response to bedtime nutrition but each individual child was consistent within himself (and not the blanket statement that warm milk produced less restless sleep in children) and so his and my results seem to be compatible.

The lack of any correlation between the predicted order of benefit from nourishment taken at bedtime and any of the orders of measured 'benefit' from flavoured drink compared with capsules, was I think due mainly to the apparently detrimental influence of this food drink on/

on the sleep of the majority of the subjects and so this may have overridden any benefit from its nutritional composition. A possible explanation might have been that when the drink mixed with stomach acid, large particles were formed and that sleep was disrupted by the mechanical irritation of these particles on the stomach wall during gastric contractions. However, when I mixed each of the three bedtime drinks with hydrochloric acid (pH 1 to 2) the resulting particles did not noticeably differ. It may be that flavoured drink was less easily digestible and was comparable to Laird and Drexel's (1934) 'hard to digest' snack at bedtime which they found led to more restless sleep than a light snack of milk and cereal.

Differences in dietary habits have been commented on before. Östberg (1973) assessed the cumulative intake of energy in one group of students that he classified by questionnaire as the more extreme morning people (early to bed, early to rise) and in another group rated as more extreme evening people (late to bed, late to rise) and he found that the evening people not only started eating later in the day (which seems logical) but also had a higher rate of food intake through the day and continued to eat until later in the evening.

Richards/

Richards (1972) studied the effect of having breakfast or nothing to eat in the morning on performance on various psychometric tests (e.g. auditory vigilance, short-term memory, coding task) in two groups of nine adult volunteers. One group comprised those who habitually took breakfast and the other group was composed of those who normally took nothing to eat in the morning. Subjects were tested five times between 1200h and 1300h and although she reported no significant differences in performance between the two experimental conditions of breakfast intake she did comment that there was a tendency toward better performances, when subjects were tested after the breakfast intake that coincided with their normal pattern.

I found no correlation between the predicted order of benefit from bedtime food and the measured orders of benefit on subjective ratings of sleep quality and this implies that there was no correlation between the subjective and objective rank orders of benefit from each of the bedtime drinks on the measures of sleep quality. Differences in sleep quality assessed while on each of the food drinks compared with subjectively rated sleep when on capsules was the only subjective rating in which I thought a correlation might be found with the predicted order of benefit based on dietary habits. Lack of correlation may be due/



due to insensitivity of the methods of getting subjective ratings. However, the visual analogue method of assessing sleep quality has been shown in our laboratory to be very sensitive to abrupt changes in sleep such as going on to or coming off hypnotic drugs, e.g. fosazepam (Allen and Oswald, 1976); mesoridazine (Adam et al., 1976). Perhaps because the changes in sleep in response to bedtime eating were less profound and may have occurred gradually, subjects' assessment of what constituted their usual sleep quality may have shifted over time. For this reason objective measurement of sleep seems superior to subjective assessment, when treatments with relatively weak effects on sleep are investigated.

To summarize, the habitual pattern of eating in the evening appeared to influence how people slept, after either capsules or a warm nutritious drink of milk or Horlicks at bedtime. Those used to taking nourishment near bedtime slept better after milk or Horlicks than after an acaloric capsule, whereas those who normally ate little or nothing at bedtime slept best after no nourishment. The people who slept better on milk also slept better on Horlicks than on capsules and similarly those who slept better on capsules than milk also slept better on capsules than when they took Horlicks at bedtime.

The/

The source of nourishment appeared to be important, for the iso-energetic flavoured drink and Horlicks had very different effects on sleep, even though they contained the same proportions of carbohydrate, protein and fat. Palatability or digestibility of the flavoured drink may be possible reasons for the difference.

TABLE 6.1. DIETARY HABITS AND SLEEP.

Ratings given to each of the 16 subjects, based on their usual eating pattern, using the first two unsuccessful methods to separate them into a rank order according to their dietary habits.

Subjects	Points awarded using the two different methods			
	Method I	Rank Order	Method II	Rank Order
KB	4	1	4	1
MC	6	2=	6	2=
MS	6	2=	6	2=
MW	6	2=	6	2=
AH	7	5=	7	5=
MT	7	5=	7	5=
RMCD	7	5=	8	7=
WH	7	5=	9	9=
JG	7	5=	9	9=
FC	8	10=	8	7=
GJ	8	10=	10	12=
AW	8	10=	10	12=
RR	9	13=	9	9=
FW	9	13=	10	12=
JR	9	13=	11	15=
GH	9	13=	11	15=

Both methods were discarded as they led to rank orders containing too many tied ranks.



TABLE 6.2. DIETARY HABITS AND SLEEP

Author's order of "predicted" benefit from bedtime nutrition

CALORIE INTAKE (Kcals) $\pm$ range									
	Whole day	1700h to 2100h	After 2100h	Total after		NZ	EMZ	Predicted Order of Benefit	
				1700h					
MC	2427 $\pm$ 190	1195 $\pm$ 80	0	1195 $\pm$ 80	0	49	16 = least		
KB	2600 $\pm$ 50	1060 $\pm$ 50	0	1060 $\pm$ 50	0	41	15		
PC	1652 $\pm$ 50	930 $\pm$ 50	20	950 $\pm$ 50	2.11	56	14		
MM	2021 $\pm$ 270	925 $\pm$ 75	20	945 $\pm$ 75	2.12	46	13		
MT	1594 $\pm$ 65	553	20	573	3.49	35	12		
MS	1990 $\pm$ 160	730 $\pm$ 75	30 $\pm$ 30	760 $\pm$ 105	3.94	37	11		
AH	1690 $\pm$ 335	715 $\pm$ 205	115 $\pm$ 15	830 $\pm$ 220	13.86	42	10		
RR	1921 $\pm$ 315	680 $\pm$ 170	135 $\pm$ 115	815 $\pm$ 285	16.56	35	9		
RMCD	2137 $\pm$ 150	591	155 $\pm$ 55	746 $\pm$ 55	20.78	28	8		
AW	3272 $\pm$ 150	1110 $\pm$ 150	305	1415 $\pm$ 150	21.56	34	7		
WH	2215 $\pm$ 507	880 $\pm$ 180	325 $\pm$ 75	1205 $\pm$ 255	26.97	40	6		
FW	2584 $\pm$ 260	795 $\pm$ 70	303	1098 $\pm$ 70	27.60	31	5		
GH	1713 $\pm$ 262	788 $\pm$ 97	305 $\pm$ 165	1093 $\pm$ 262	27.90	46	4		
GJ	2511 $\pm$ 40	985 $\pm$ 40	390	1375 $\pm$ 40	28.36	39	3		
JR	2327 $\pm$ 42	1023 $\pm$ 42	437	1460 $\pm$ 42	29.93	44	2		
JG	2766 $\pm$ 60	910	636 $\pm$ 35	1546 $\pm$ 35	41.14	33	1 = most		

TABLE 6.3. DIETARY HABITS AND SLEEP  
Dietician's order of "predicted" benefit from bedtime nutrition

		CALORIE INTAKE (kcal/s)					Predicted Order of Benefit
		Whole day	1700h to 2100h	After 2100h	Total after 1700h	N%	
MC	m	2326	963	0	963	0	41
KB	m	2221	711	0	711	0	32
PC	f	1593	789	19	808	2.35	50
MM	f	1605	636	19	655	2.90	40
MS	f	1819	831	33	864	3.82	46
MT	f	1547	445	19	464	4.10	29
AM	f	1755	756	138	894	15.44	43
RR	f	1723	668	141	809	17.43	39
AW	m	2734	1013	239	1252	19.09	37
EMCD	f	1864	506	120	626	19.17	27
WH	m	2306	1027	317	1344	23.59	45
FW	f	2502	711	256	967	26.47	28
GJ	m	2036	767	319	1086	29.37	38
JR	f	2165	920	453	1373	32.99	43
GH	f	1557	656	345	1001	34.47	42
JG	m	2738	716	490	1206	40.63	26

m = male  
f = female

1 = most



TABLE 6.4. DIETARY HABITS AND SLEEP

Correlation between the Author's and the independent Dietician's rank orders of predicted benefit from bedtime nutrition based on the 16 subjects'diet diaries.

Predicted order of benefit from bedtime nutrition

Subjects	Dietician's rank order*	Author's rank order**
MC	1	1
KB	2	2
FC	3	4
MW	4	3
MS	5	6
MT	6	5
AH	7	7
RR	8	8
AW	9	10
RMCD	10	9
WH	11	11
FW	12	12
GJ	13	14
JR	14	15
GH	15	13
JG	16	16

Spearman's rank correlation,  $df = 14$ .

$r_s = 0.982$ ,  $t = 19.63$ ,  $p < 0.00002$ , 1-tailed

\*:- calculations in Table 6.3

\*\*:- " " " 6.2



TABLE 6.5. DIETARY HABITS AND SLEEP : WHOLE NIGHT MEASURES

Total sleep time (TST).

Measured benefit from each of the three bedtime food drinks in comparison with capsules.

Each value for each of 16 subjects is the mean TST over 5 nights on the food drink minus the mean TST over the 5 nights recorded while on capsules. (Raw data in Table 5.1).

The rank orders are in descending order of benefit from bedtime nutrition: 1= most to 16= least.

Differences in mean total sleep time:  $\Delta$  min.

Subjects	Rank Order of N% Score	Flavoured drink - capsules		Milk - capsules		Horlicks - capsules	
		$\Delta$ min	Rank order	$\Delta$ min	Rank order	$\Delta$ min	Rank order
KB	15	16.6	2	- 2.0	11	1.3	10
MC	16	-20.0	11	- 50.8	5	-40.6	16
FC	14	5.8	6	12.7	8	2.2	9
JG	1	7.5	4	50.8	1	3.3	8
GH	2	7.2	5	17.7	5	29.4	2
AW	10	- 9.0	10	16.1	7	7.6	5
WH	6	- 8.8	9	17.5	6	- 4.4	12
GJ	4	2.1	7	6.0	10	5.1	7
RMCD	7	-48.1	16	30.9	2	29.8	1
JR	3	10.6	3	19.3	4	20.0	4
RR	9	-37.9	14	- 4.0	12	1.0	11
MS	12	-24.7	12	- 40.1	14	-16.7	14
MT	11	-25.5	13	9.7	9	6.8	6
FW	5	-44.7	15	- 19.6	3	-13.6	13
AW	8	36.7	1	30.8	3	24.6	3
MW	13	- 1.3	8	- 67.5	16	-34.8	15

Spearman's rank correlations ( $r_s$ ): df = 14 (2-tailed)

Ranked benefit from:

	Flavoured drink	Milk	Horlicks
Ranked N% scores	0.15 (n.s.)	0.64, $p < 0.01$	0.51, $p < 0.01$
Ranked benefit from milk	-	-	0.82, $p < 0.001$

TABLE 6.6. DIETARY HABITS AND SLEEP : WHOLE NIGHT MEASURES

Total wakefulness occurring after the first onset of sleep and before the end of the recording (TWT).

Measured benefit from each of the three bedtime drinks in comparison with capsules.

Each value for each of 16 subjects is the mean TWT over 5 nights on capsules minus the mean TWT over the 5 nights recorded on the food drink. (Raw data in Table 5.2).

The rank orders are in descending order of benefit from bedtime nutrition: 1 = most to 16 = least.

Differences in mean total waketime:  $\Delta$  min.

Subjects	Rank Order of N% Score	Capsules - Flav. drink		Capsules - Milk		Capsules - Horlicks	
		$\Delta$ min	Rank order	$\Delta$ min	Rank order	$\Delta$ min.	Rank order
KB	15	12.3	3	- 8.2	12	1.1	11
MC	16	- 7.0	10	-25.2	14	-29.9	16
FC	14	9.1	5	12.0	5.5	4.5	9
JG	1	9.2	4	61.5	1	2.8	10
GH	2	-10.1	11	- 9.0	13	20.3	3
AH	10	- 4.2	9	9.8	7	7.0	5
WH	6	- 1.2	7	21.3	4	5.4	7
GJ	4	0.2	6	6.2	8	6.9	6
RMCD	7	-36.7	15	28.0	3	25.7	2
JR	3	13.3	2	12.0	5.5	11.3	4
RR	9	-35.3	13	0.6	9	5.0	8
MS	12	-26.3	12	-35.8	15	-18.9	15
MT	11	-35.6	14	- 3.6	11	- 4.4	12
FW	5	-43.5	16	- 2.8	10	-10.4	13
AW	8	35.2	1	32.8	2	28.3	1
MW	13	- 3.6	8	-39.6	16	-14.6	14

Spearman's rank correlations ( $r_s$ ): df = 14 (2-tailed)

Ranked benefit from:

	Flav. drink	Milk	Horlicks
Ranked N% score	0.06 (n.s.)	0.51, $p < 0.05$	0.55, $p < 0.05$
Ranked benefit from milk	-	-	0.66, $p < 0.01$



TABLE 6.7. DIETARY HABITS AND SLEEP : FIRST 6h TOTALS.

Intervening wakefulness occurring in the accumulation of the first 6h of sleep.

Measured benefit from each of the three bedtime food drinks in comparison with capsules.

Each value for each of 16 subjects is the mean min of intervening wakefulness (IW) over 5 nights on capsules minus the mean min IW over 5 nights recorded on the food drink. (Raw data in Table 5.8).

The rank orders are in descending order of benefit from bedtime nutrition: 1 = most to 16 = least.

Differences in mean min IW in 1st 6h sleep:  $\Delta$  min.

Subjects	Rank order of NZ score	Capsules - Flavoured drink $\Delta$ min	Rank order	Capsules - Milk $\Delta$ min	Rank order	Capsules - Horlicks $\Delta$ min	Rank order
MW	13	4.6	6	-59.4	16	- 5.5	13
AW	8	23.1	1	15.2	4	12.2	5
AH	10	- 3.8	9	8.4	5	6.5	6
KB	15	14.2	3	- 8.1	12	- 2.6	12
JR	3	21.2	2	16.3	3	16.0	3
JG	1	10.1	4	34.6	1	45.4	1
GH	2	-13.9	12	-13.9	13	14.0	4
WH	6	- 4.5	10	0.8	7	4.3	7
MT	11	-50.3	15	- 7.7	11	- 6.3	14
RMCD	7	-44.8	13	25.9	2	33.4	2
FC	14	5.5	5	5.4	6	3.5	8
MC	16	-11.5	11	-44.0	14	-53.7	16
GJ	4	- 3.2	8	- 3.0	9	0.0	10
MS	12	- 1.8	7	-49.2	15	- 0.6	11
FW	5	-60.2	16	0.3	8	- 8.6	15
RR	9	-45.0	14	- 6.4	10	0.8	9

Spearman's rank correlations ( $r_s$ ): df = 14 (2-tailed)

Ranked benefit from:

	Flavoured drink	Milk	Horlicks
Ranked NZ score	-0.05 (n.s.)	0.53, $p < 0.05$	0.64, $p < 0.01$
Ranked benefit from milk	-	-	0.74, $p < 0.002$



TABLE 6.8. DIETARY HABITS AND SLEEP : FIRST 3 h TOTALS

Intervening wakefulness occurring in the accumulation of the first 3 h of sleep.

Each rank for each of 16 subjects is based on the mean difference in min of intervening wakefulness (IW) over 5 nights on capsules minus the mean IW over 5 nights recorded on the food drink. (Raw data in Table 5.13). The rank orders are in descending order of benefit from bedtime nutrition: 1 = most to 16 = least.

Ranked differences : mean min IW in 1st 3 h sleep

Subjects	Rank order of N% score	Capsules - Flavoured drink	Capsules - Milk	Capsules - Horlicks
KB	15	10	13	13
MC	16	5	14	15
FC	14	3	5	7
JG	1	6	11	12
GH	2	12	15	3
AH	10	11	4	5
WH	6	7	6	6
GJ	4	4	12	10.5
RMCD	7	13	3	1
JR	3	1	2	2
RR	9	16	9	8
MS	12	8	10	10.5
MT	11	15	7	9
FW	5	14	8	16
AW	8	2	1	4
MW	13	9	16	14

Spearman's rank correlations ( $r_s$ ): df = 14 (2-tailed)

Ranked benefit from:

	Flavoured drink	Milk	Horlicks
Ranked N % score	0.05 (n.s.)	0.17 (n.s.)	0.38 (n.s.)
Ranked benefit from milk	-	-	0.65, $p < 0.01$

TABLE 6.9. DIETARY HABITS AND SLEEP : SECOND 3 h TOTALS

Intervening wakefulness occurring in the accumulation of the second 3h of sleep.

Each rank for each of 16 subjects is based on the mean difference in min of intervening wakefulness (IW) over 5 nights on capsules minus the mean IW over 5 nights recorded on the food drink. (Raw data in Table 5.13).

The rank orders are in descending order of benefit from bedtime nutrition: 1 = most to 16 = least.

Ranked differences: mean min IW in 2nd 3h sleep

Subjects	Ranked NZ Score	Capsules - Flavoured drink	Capsules - Milk	Capsules - Horlicks
KB	15	1	5	12
MC	16	13	15	16
FC	14	6	7	4
JG	1	2	1	1
CH	2	10	3.5	13
AH	10	4	3.5	8
WH	6	8	10	5
GJ	4	9	11	9
RMCD	7	15	2	2
JR	3	11	6	15
RR	9	12	12	10
MS	12	5	16	11
MT	11	14	13	14
FW	5	16	8	3
AW	8	7	9	7
MW	13	3	14	6

Spearman's rank correlations ( $r_s$ ) : df = 14 (2-tailed)

Ranked benefit from:

	Flavoured drink	Milk	Horlicks
Ranked NZ score	-0.20 (n.s.)	0.51, $p < 0.05$	0.27 (n.s.)
Ranked benefit from milk	-	-	0.41 (n.s.)



TABLE 6.10. DIETARY HABITS AND SLEEP : FIRST 6h TOTALS.

Total min of intervening wakefulness plus total min of stage 1 in the accumulation of the first 6h of sleep (IW + stg.1).

Measured benefit from each of the three bedtime drinks in comparison with capsules.

Each value for each of 16 subjects is the mean (IW + stg.1) over 5 nights on capsules minus the mean (IW + stg.1) over the 5 nights recorded on the food drink. (Raw data in Table 5.9).

The rank orders are in descending order of benefit from bedtime nutrition: 1 = most to 16 = least.

Differences in mean min (IW + stg.1) in 1st 6h:  $\Delta$  min

Subjects	Ranked N% score	Capsules - Flavoured drink		Capsules - Milk		Capsules - Horlicks	
		$\Delta$ min	Rank order	$\Delta$ min	Rank order	$\Delta$ min	Rank order
MW	13	0.3	6	-68.4	16	-13.9	13
AW	8	26.2	1	18.7	3	17.6	4
AH	10	- 0.2	7	11.6	5	14.3	5
KB	15	- 4.2	10	-22.3	13	-18.6	14
JR	3	15.9	2	9.9	6.5	19.1	3
JG	1	6.9	3	21.5	2	41.8	1
GH	2	-14.5	12	-16.7	11	13.7	6
WH	6	0.8	5	9.9	6.5	9.3	7
MT	11	-66.7	15	-18.6	12	-19.2	15
RMCD	7	-46.6	13	27.5	1	33.4	2
FC	14	5.5	4	14.6	4	5.8	8
MC	16	-12.4	11	-44.4	14	-55.8	16
GJ	4	- 0.5	9	-11.9	9	1.5	9
MS	12	- 0.3	8	-58.5	15	1.3	10
FW	15	-83.8	16	- 2.4	8	-11.8	12
RR	9	-58.1	14	-14.0	10	- 2.1	11

Spearman's rank correlations ( $r_s$ ): df = 14 (2-tailed)

Ranked benefit from:

	Flavoured drink	Milk	Horlicks
Ranked N% scores	0.12 (n.s.)	0.50, $p < 0.05$	0.68, $p < 0.01$
Ranked benefit from milk	-	-	0.83, $p < 0.001$



TABLE 6.11. DIETARY HABITS AND SLEEP.

Lack of correlation between the order of receiving the four treatments and the mean total min of intervening wakefulness in the accumulation of the first 6h of sleep.

Each value for each of 16 subjects is the mean of 5 nights.

Mean min intervening wakefulness in 1st 6h on each treatment arranged in chronological order.

Subjects	First treatment	Second treatment	Third treatment	Fourth treatment
AW	8.3 (B)	31.4 (A)	19.2 (D)	16.2 (C)
MW	71.1 (C)	17.2 (D)	7.1 (B)	11.7 (A)
AH	11.2 (D)	9.3 (C)	17.7 (A)	21.5 (B)
KB	25.3 (A)	11.1 (B)	33.4 (C)	27.9 (D)
JR	24.1 (B)	45.3 (A)	29.3 (D)	29.0 (C)
JG	13.6 (C)	2.8 (D)	38.1 (B)	48.2 (A)
GH	8.3 (D)	36.2 (C)	22.3 (A)	36.2 (B)
WH	20.0 (A)	24.5 (B)	19.2 (C)	15.7 (D)
MT	73.5 (B)	23.2 (A)	29.5 (D)	30.9 (C)
RMCD	30.6 (C)	23.1 (D)	101.3 (B)	56.5 (A)
FC	8.4 (D)	6.5 (C)	11.9 (A)	6.4 (B)
MC	20.7 (A)	32.2 (B)	64.7 (C)	74.4 (D)
GJ	3.2 (B)	0.0 (A)	0.0 (D)	3.0 (C)
MS	49.2 (C)	0.6 (D)	1.8 (B)	0.0 (A)
RR	2.4 (D)	9.6 (C)	3.2 (A)	48.2 (B)
FW	17.9 (A)	78.1 (B)	17.6 (C)	26.5 (D)
Mean $\pm$ S.D.	24.2 $\pm 22.1$	21.9 $\pm 20.2$	26.0 $\pm 25.8$	28.3 $\pm 28.6$

Friedman's Analysis of Variance by ranks

$$\chi^2_r = 1.031, \text{ df} = 3 \text{ (n.s.)}$$

NOTE: treatment in parenthesis:

A = Capsules;            B = Flavoured drink  
C = Milk                D = Horlicks

TABLE 6.12. DIETARY HABITS AND SLEEP.

Lack of correlation between the order of receiving the four treatments and the mean total min of wakefulness occurring after the first onset of sleep and before the end of the recording (TWT).

Each value for each of 16 subjects is the mean of 5 nights.

Mean TWT on each treatment arranged in chronological order				
Subjects	First treatment	Second treatment	Third treatment	Fourth treatment
AW	22.6 (B)	57.8 (A)	29.5 (D)	25.0 (C)
MW	65.4 (C)	40.4 (D)	29.4 (B)	25.8 (A)
AH	12.8 (D)	9.9 (C)	19.0 (A)	24.0 (B)
KB	33.0 (A)	20.7 (B)	41.2 (C)	31.9 (D)
JR	36.3 (B)	49.6 (A)	38.3 (D)	37.6 (C)
JG	29.0 (C)	87.7 (D)	81.3 (B)	90.5 (A)
GH	12.1 (D)	41.4 (C)	32.4 (A)	42.5 (B)
WH	55.1 (A)	56.3 (B)	33.8 (C)	49.7 (D)
MT	84.6 (B)	49.0 (A)	53.4 (D)	52.6 (C)
RMCD	42.7 (C)	45.0 (D)	107.4 (B)	70.4 (A)
FC	23.4 (D)	15.9 (C)	27.9 (A)	18.8 (B)
MC	81.6 (A)	88.6 (B)	106.8 (C)	111.5 (D)
GJ	15.0 (B)	15.2 (A)	8.3 (D)	9.0 (C)
MS	92.8 (C)	75.9 (D)	83.3 (B)	57.0 (A)
RR	6.8 (D)	11.2 (C)	11.8 (A)	47.1 (B)
FW	29.2 (A)	72.7 (B)	32.0 (C)	39.6 (D)
Mean	40.2	46.1	46.0	45.8
$\pm$ S.D.	$\pm 27.7$	$\pm 26.5$	$\pm 31.6$	$\pm 26.8$

Friedman's Analysis of Variance by ranks

$$X_r^2 = 1.88, \quad df = 3 \quad (n.s.).$$

NOTE: treatment in parenthesis:

A = Capsules

B = Flavoured drink

C = Milk

D = Horlicks



TABLE 6.13. DIETARY HABITS AND SLEEP : SUBJECTIVE RATINGS OF SLEEP QUALITY.

Measured differences between each of the three bedtime drinks and capsules. Each value for each of 16 subjects is the mean sleep quality rating over the 6 laboratory nights on the food drink minus the mean rating for the 6 nights on capsules. The differences listed below are based on the data used to compile Table 5.16, but using the data when it was to one decimal place. This was done to reduce the number of tied ranks.

Rank orders are in descending order of benefit from bedtime nutrition:

1 = most to 16 = least.

Subjects	Ranked N% score	Differences in mean sleep quality ratings: $\Delta$ mm					
		Flavoured drink		Milk		Horlicks	
		$\Delta$ mm	Rank order	$\Delta$ mm	Rank order	$\Delta$ mm	Rank order
AW	8	0.3	8	- 0.3	7.5	0.7	6
MW	13	4.0	4	0.5	6	2.4	4
AH	10	- 0.5	10	- 5.7	13	- 7.8	15
KB	15	0.1	9	- 2.7	10	1.0	5
JR	3	4.3	3	15.3	1	- 0.4	8
JG	1	- 5.8	14	- 5.8	14	5.7	1
GH	2	5.5	2	- 1.4	9	- 5.9	14
WH	6	3.1	5	11.5	2	5.6	2
MT	11	- 5.7	13	- 3.5	11	- 2.9	11
RMCD	7	-12.0	15	-10.9	15	- 3.2	12
FC	14	8.2	1	5.8	4	- 3.5	13
MC	16	3.0	6	- 0.3	7.5	0.5	7
GJ	4	- 3.5	11	3.9	5	3.0	3
FW	5	- 4.0	12	6.0	3	- 1.4	9
RR	9	2.8	7	- 4.7	12	- 2.8	10
MS	12	-20.3	16	-21.0	16	-27.5	16

Spearman's rank correlations ( $r_s$ ): df = 14 (2-tailed).

Ranked benefits from:

	Flavoured drink	Milk	Horlicks
Ranked N% scores	-0.09 (n.s.)	0.14 (n.s.)	0.21 (n.s.)



CHAPTER 7

DIFFERENCES IN THE RESPONSES TO BEDTIME NUTRITION IN  
A GROUP OF BEDTIME 'EATERS' AND IN A GROUP OF BEDTIME  
'NON-EATERS'

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## CHAPTER 7

### SUMMARY

A group of eight subjects who usually had something to eat at bedtime were found to sleep better after milk or Horlicks than after an inert capsule, whereas a group of eight subjects who normally had little or nothing to eat prior to retiring to bed, tended to sleep best after the inert capsule.

## INTRODUCTION

Březinová and Oswald (1972) found that sleep after the bedtime food drink Horlicks was significantly less broken than sleep after a placebo pill at bedtime. In view of the findings described in the previous chapter it is possible that in their study eight volunteers were selected who usually had something to eat at bedtime. And as their subjects were also instructed not to eat or drink anything after 1900h except the treatment then their results may be due largely to the detrimental effects on sleep of lack of food on the nights when the placebo pill was taken.

The following calculations were undertaken to see if I could replicate the findings of Březinová and Oswald (1972), using the data collected during the experiment described in Chapter 5.



## METHODS

The 16 subjects in the experiment were divided into two groups of eight according to their N% scores (Table 6.3 previous chapter). One group comprised those ranked 1 to 8 according to their N% scores and thus were the eight subjects who normally ate relatively more food at bedtime. These eight subjects were called the bedtime 'Eaters' group whereas those ranked 9-16 according to their N% scores were the 'Non-Eaters' group.

The mean total sleep time, the mean min of intervening wakefulness accumulated in the first 6h of sleep and the mean min of intervening wakefulness plus the mean min of stage 1 in the first 6h of sleep were computed for each subject for the five nights recorded when taking each of the four bedtime treatments (capsules, flavoured drink, milk and Horlicks).

The mean min of each of the above sleep measures were calculated for the bedtime Eaters group and the bedtime Non-Eaters group. Sleep after each of the three bedtime food drinks was compared (within each group) with sleep after capsules by means of t-tests for paired observations (Ferguson, 1959). The bedtime Eaters group was predicted to sleep better after Horlicks than/

than after capsules and so 1-tailed levels of significance were employed for comparisons between Horlicks and capsules, other comparisons within the two groups had no prior grounds for predictions and so 2-tailed levels of significance were used.

## RESULTS

### (a) Total sleep time (Table 7.1)

The members of the bedtime Eaters group slept significantly longer after both milk and Horlicks when compared with their sleep after capsules. Whereas those in the Non-Eaters group slept longest when on capsules but, the comparisons failed to reach statistical significance. The comparisons between the flavoured drink and capsules were significantly insignificant for both groups.

### (b) Intervening wakefulness in first 6h of sleep (Table 7.2)

The first six hours of accumulated sleep of the bedtime Eaters group was less broken by wakefulness after Horlicks than when they had taken capsules at bedtime, but the level of significance was only 5% and so this can only be regarded as a trend. The sleep of the bedtime Non-Eaters group was least broken after capsules at bedtime. However the variance was high and the comparisons between sleep after the bedtime food drinks with capsules in the Non-Eater group were not statistically significant.



(c) Intervening wakefulness plus stage 1 in the first six hours of sleep (Table 7.3).

Subjects in the bedtime Eaters group had significantly less ( $p < 0.025$ ) intervening wakefulness plus stage 1 in the accumulation of the first 6h of sleep after Horlicks at bedtime when compared with their sleep after capsules. The comparisons between milk or flavoured drink and capsules were not significantly different.

The bedtime Non-Eaters sleep was least interrupted by waking and periods of drowsiness on the nights they took capsules at bedtime, however only the comparison between capsules and milk reached the 5% level of significance and so the results only indicate a tendency for their sleep to have been more broken after food at bedtime.

## DISCUSSION

The intention of this Chapter was to explore the possibility that the apparent disparity between my results and those of Březinová and Oswald (1972), in the effects on sleep of Horlicks when compared with capsules, might be due to differences in the dietary habits of the subjects.

The 1-tailed level of significance was regarded as justified for the comparisons between capsules and Horlicks as these had been predicted. However, any conclusions put forward from this post-hoc treatment of the data are only pointers for future research which may confirm or otherwise these tentative findings.

The data collected from the bedtime Eaters group showed that these eight subjects slept significantly longer and their sleep tended to be less broken by wakefulness in the first 6h of sleep when they took Horlicks at bedtime when compared with sleep after capsules. These results are in the same direction as those of Březinová and Oswald (1972), and so suggest that their eight subjects were a group of people who normally had something to eat or drink at bedtime. It may be that those who usually eat at bedtime would more readily volunteer to take part in a study involving eating at bedtime.

The/

The bedtime Non-Eater group slept longest and had least interruption of their sleep by waking when they took capsules at bedtime, however, none of the comparisons reached statistical significance.

Inspection of Table 6.3 (previous Chapter) shows that the division of subjects into two groups of eight according to the rank orders of their N% score was rather arbitrary and included two subjects in the Non-Eater group who in fact normally ate at bedtime (AH and RR). However this division of subjects was done post-hoc and so I did not feel entitled to divide the subjects into groups in any other way.

It would be interesting to compare sleep after capsules with sleep after Horlicks in subjects pre-selected into one group who normally ate a lot and another group who eat nothing at bedtime. I would predict that with these highly polarized groups clear differences would emerge and the Non-Eater group would sleep significantly worse after food at bedtime.

The main conclusion to be drawn from this post-hoc inspection of my data is that you can probably influence the results of experiments into nutrition and sleep, by the selection of suitable subjects.



TABLE 7.1. BEDTIME EATERS/NON-EATERS

Differences between the bedtime (a) Eaters group and (b) Non-eaters group in the mean total min asleep (total sleep time), when taking each of the four bedtime treatments.

Each value is the mean of 40 subject-nights: Eight subjects in each group recorded for 5 nights on each treatment.

(a) Bedtime Eaters (NZ scores 19% to 41%)

n = 8

mean $\pm$ S.D. min - total time asleep			
Capsules	Flavoured drink	Milk	Horlicks
452.0 $\pm 25.5$	447.3 $\pm 36.5$	471.2 $\pm 19.1$	463.8 $\pm 25.1$

t-tests for paired observations, df = 7

	Flavoured drink	Milk	Horlicks
Capsules	t = 0.46 (n.s.)	t = 2.64, p < 0.05 (2t)	t = 2.03, p < 0.05 (1t)
	2t = 2-tailed:	1t = 1-tailed level	

(b) Bedtime Non-eaters (NZ scores 0 to 17%)

n = 8

mean $\pm$ S.D. min - total time asleep			
Capsules	Flavoured drink	Milk	Horlicks
458.2 $\pm 25.4$	446.2 $\pm 29.3$	442.4 $\pm 47.1$	449.0 $\pm 38.2$

t-tests for paired observations, df = 7 (2-tailed)

	Flavoured drink	Milk	Horlicks
Capsules	t = 1.86 (n.s.)	t = 1.38 (n.s.)	t = 1.35 (n.s.)

NOTE: Individual subjects data listed in Table 5.1.

TABLE 7.2. BEDTIME EATERS/NON-EATERS

Differences between the bedtime (a) Eaters group and (b) Non-eaters group in the mean total min of intervening wakefulness occurring in the accumulation of the first 6 h of sleep, when taking each of the four bedtime treatments.

Each value is the mean of 40 subject-nights: Eight subjects in each group recorded for 5 nights on each treatment.

(a) Bedtime Eaters (n = 8)

Mean  $\pm$  S.D. min intervening wakefulness in 1st 6 h sleep

Capsules	Flavoured drink	Milk	Horlicks
30.2 $\pm$ 18.8	39.1 $\pm$ 34.1	20.7 $\pm$ 10.7	15.6 $\pm$ 10.9

t-tests for paired observations, df = 7

	Flavoured drink	Milk	Horlicks
Capsules	t = 0.83 (n.s.)	t = 1.66 (n.s.)	t = 2.35, p<0.05*

\*not statistically significant

(b) Bedtime Non-eaters (n = 8)

Mean  $\pm$  S.D. min intervening wakefulness in 1st 6 h sleep

Capsules	Flavoured drink	Milk	Horlicks
14.2 $\pm$ 9.2	25.2 $\pm$ 24.9	34.3 $\pm$ 25.4	21.5 $\pm$ 23.9

t-tests for paired observations, df = 7 (2-tailed)

	Flavoured drink	Milk	Horlicks
Capsules	t = 1.30 (n.s.)	t = 2.15 (n.s.)	t = 1.06 (n.s.)

Note: Individual subjects data listed in Table 5.8



TABLE 7.3. BEDTIME EATERS/NON-EATERS

Differences between the bedtime (a) Eaters group and (b) non-eaters group in the mean total min of intervening wakefulness plus the mean total min of stage 1 occurring in the accumulation of the first 6 h of sleep, when taking each of the four bedtime treatments.

Each value is the mean of 40 subject-nights: Eight subjects in each group recorded for 5 nights on each treatment.

(a) Bedtime Eaters (n = 8)

mean  $\pm$  S.D. min interv. wake + stg 1 in 1st 6 h sleep

Capsules	Flavoured drink	Milk	Horlicks
65.1 $\pm 23.2$	77.1 $\pm 41.2$	58.1 $\pm 12.3$	49.6 $\pm 18.9$

t-tests for paired observations, df = 7

	Flavoured drink	Milk	Horlicks
Capsules	t = 0.93 (n.s.)	t = 1.23 (n.s.)	t = 2.60, p < 0.025*

\*1-tailed level of significance

(b) Bedtime Non-eaters (n = 8)

mean  $\pm$  S.D. min interv. wake + stg 1 in 1st 6 h sleep

Capsules	Flavoured drink	Milk	Horlicks
45.1 $\pm 19.4$	62.1 $\pm 33.4$	71.2 $\pm 33.5$	56.2 $\pm 37.8$

t-tests for paired observations, df = 7 (2-tailed)

	Flavoured drink	Milk	Horlicks
Capsules	t = 1.68 (n.s.)	t = 2.35, p < 0.05†	t = 1.45 (n.s.)

† = not significant

NOTE: Individual subjects data listed in Table 5.9



CHAPTER 8

CORRELATION BETWEEN BODY WEIGHT AND AMOUNT OF REM SLEEP

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## CHAPTER 8

### SUMMARY

The body weights of 16 middle-aged subjects were found to be highly correlated with their average quotas of REM sleep. This was true of the mean total min of REM sleep accumulated over the whole night, the mean min of REM sleep accumulated in the first 6h of sleep and the mean total min of REM sleep as a percentage of the total time spent asleep.

## INTRODUCTION

The association between REM sleep and the bizarre mental life of dreams has led to an emphasis of research interest upon psychological correlates of REM sleep and a neglect of attention toward somatic functions for REM sleep. Attempts to find any correlations between personality and REM sleep have been unsuccessful (reviewed by Foulkes, 1966).

A number of investigations have shown that the amount of REM sleep is reduced in mental retardates (e.g. Petre-Quadens and Jouvet, 1966), that babies have very large amounts of REM sleep at the time when their brains are maturing rapidly (Roffwarg et al., 1966) and that when information processing is reduced, as might be expected, in severely deaf children, the amount of REM sleep is below normal levels (Stojanovic and Dürri<sup>1</sup>, 1975).

After poisoning by CNS-affecting drugs there is an increase in the amount of REM sleep lasting for many weeks, suggesting that REM sleep is associated with repair processes in the brain (Oswald, 1969; Haider and Oswald, 1970). All of these findings point to a role for REM sleep in brain function and metabolism and in consequence investigations into and speculations about/



about the function of REM sleep have tended to think only of the brain (Oswald, 1969, 1970; Hartmann, 1973; Stern and Morgane, 1974). Yet during REM sleep muscle tone in the body is at its lowest (Jacobson et al., 1964; Pompeiano, 1967), which means less cellular work is being done in the muscles and (if the theory put forward in Chapter 1 of this thesis is correct) synthetic, restorative processes will then be promoted. This suggests that REM sleep may also have a role in bodily repair processes more general than the brain alone. Such a role has previously been proposed for slow wave sleep (Oswald, 1969, 1970; Hartmann, 1973).

The sleep pattern of any one individual can vary considerably from night to night and to obtain a reliable measure of a person's sleep many, and preferably consecutive, recordings should be made, because one night's sleep can be unrepresentative as it depends on how a person slept on previous nights. This is particularly true of REM sleep, which of all the sleep stages is the most vulnerable to disruption and the amount recorded is reduced by a variety of different treatments or environmental circumstances.

The data generated by the experiment described earlier in Chapter 5 appeared well suited to an investigation of REM sleep. The subjects were well adapted to/

to the laboratory procedure, in fact, 14 out of 16 of the subjects had previously participated in at least one other sleep study.

Body weight and daily metabolic rate are highly correlated when both are in logarithmic form (Kleiber, 1961) and so the present investigation was undertaken to see if body weight (and so daily metabolism) was related to mean amounts of REM sleep, slow wave sleep or total sleep time. The latter was shown to be correlated with metabolic rate (rate/kg) in a study across 53 animal species (Zepelin and Rechtschaffen, 1974).

## METHODS

### (a) Subjects and electrophysiological recordings

There were 16 subjects of average age 59y (52 to 67y). The group comprised ten women and six men. Each slept in the laboratory on six consecutive nights (1 adaptation and 5 recordings) every four weeks during a 13-week period, making 20 nights in all. Lights-out was from 2215h  $\pm$  15 min to 0700h  $\pm$  15 min and all recordings lasted the same length of time - 8.75h.

The 320 electrophysiological records were scored into the various sleep stages and wakefulness in terms of the usual criteria (Rechtschaffen and Kales, 1968). The amounts of stages 3+4 and REM sleep on each night were computed and the means for each subject for his or her 20 nights were calculated. The same was done for the total amount of time that subjects were asleep during the recording.

### (b) Body weight measured

On the first and last nights of each week of attendance subjects were weighed, by the investigator, in light indoor clothing. The eight weight measures (in lbs) were averaged for each person.

The mean weight was converted into kg by multiplying the weight in lbs by 0.454. The mean weights in kg were also converted into logarithmic form.



Pearson's product-moment correlation coefficient (Ferguson, 1959) was calculated to test the significance of the relationship between various measures of sleep and body weight.

Two-tailed levels of significance are quoted for all the results except for the correlation between total min REM sleep and total sleep time where there was a prediction of a positive correlation.

Linear regression by the method of least squares (Ferguson, 1959) was used to fit a straight line through the graphically presented data points.

## RESULTS

### (a) Mean body weight of subjects

The 16 subjects covered a wide range of body weight i.e. 104 lb to 202 lb (47kg to 92kg), but the individual weights varied little over the eight separate weighings e.g. the largest standard deviation for any subject's weight was 2.46 lb over 13 weeks (Table 8.1).

### (b) Correlations (r) between body weight and REM sleep

Body weight was found to be significantly correlated with the mean total min of REM sleep whether the mean of all 20 nights recorded per subject was used:  $r = 0.633$ ,  $p < 0.01$  (Table 8.2 and Figure 8.1), or the means of the five nights on each of the four bedtime treatments (Table 8.3). There were no significant differences among the mean min of REM sleep accumulated during administration of the four bedtime treatments (Table 5.11 Chapter 5). Subjects slept, on average, for differing lengths of time and the amount of REM sleep was related to the total length of time that subjects slept:  $r = 0.481$ ,  $p < 0.05$ , 1-tailed (Table 8.2), but body weight and percentage of total sleep spent in REM sleep were more highly correlated:  $r = 0.631$ ,  $p < 0.01$  (Table 8.2 and Figure 8.2) and body weight was not significantly correlated/

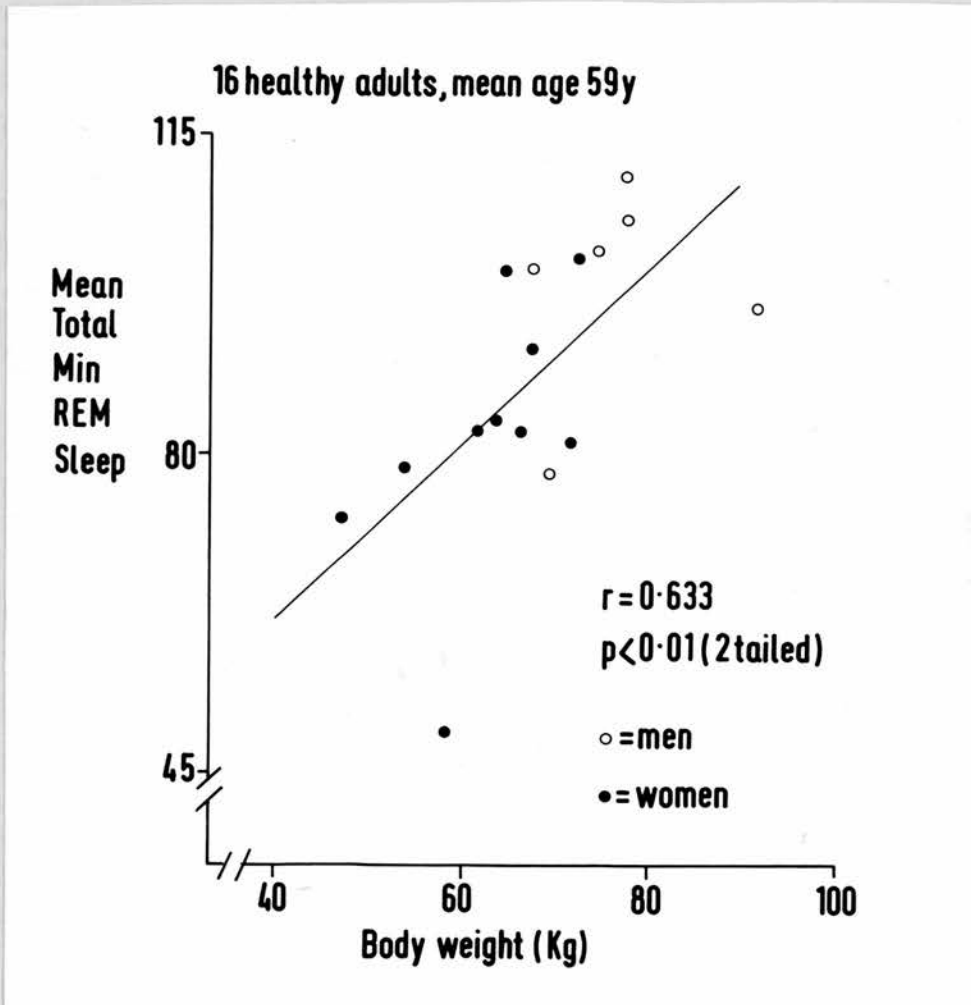


FIGURE 8.1 Correlation between mean total min of REM sleep and body weight in 16 middle-aged subjects.

Each value of total REM sleep is the mean of 20 recorded nights.



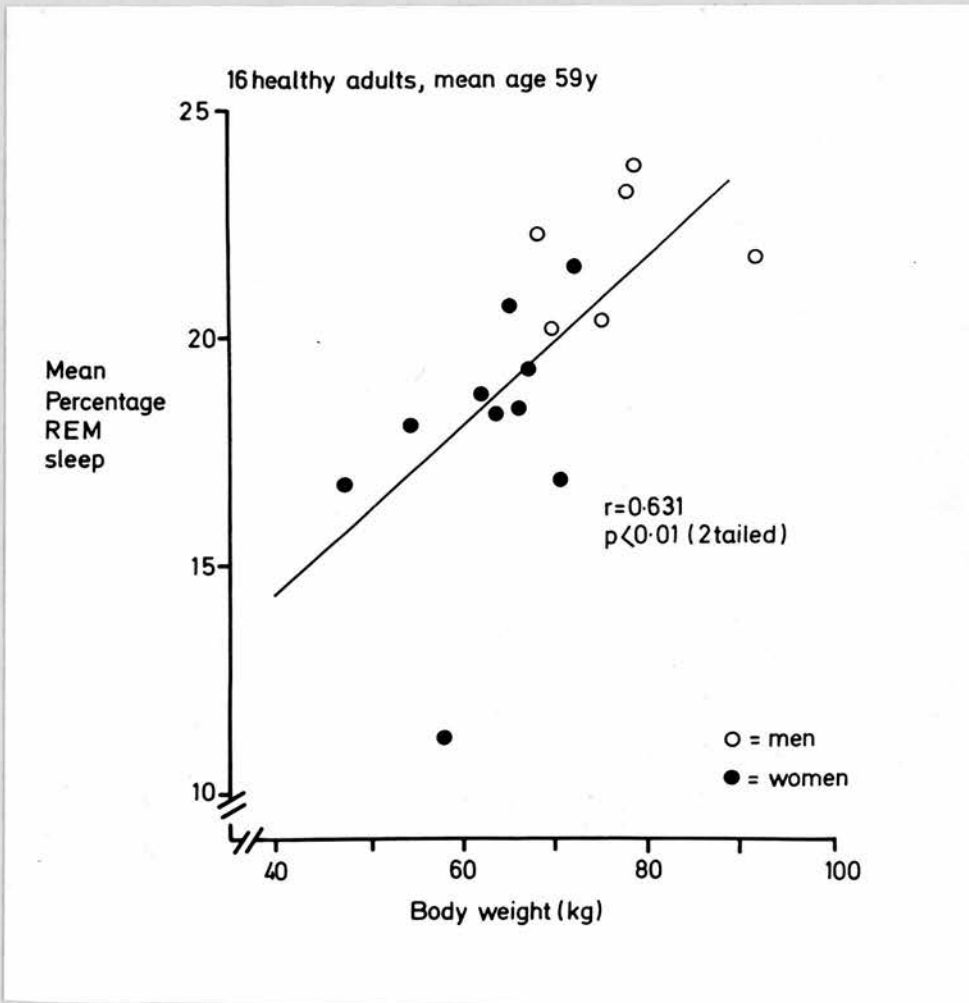


FIGURE 8.2 Correlation between mean percentage REM sleep and body weight in 16 middle-aged subjects.

Each value of % REM sleep is the mean of 20 recorded nights.

correlated with the mean total time that subjects were asleep (Table 8.2).

The relationship between body weight and REM sleep was equally significant, when the min of REM sleep accumulated in the first 6h of sleep were considered:  $r = 0.651$ ,  $p < 0.01$  (Table 8.2).

(c) Correlations ( $r$ ) between log body weight and REM sleep.

Log body weight was significantly correlated with the mean total min of REM sleep:  $r = 0.645$ ,  $p < 0.01$  (Table 8.4 and Figure 8.3) and with the percentage of total time asleep spent in REM sleep:  $r = 0.634$ ,  $p < 0.01$  (Table 8.4 and Figure 8.4).

(d) Correlations ( $r$ ) between body weight, total sleep time, slow wave sleep (SWS) and percentage SWS.

Table 8.5 lists the inter-correlations between mean body weight, total sleep time, total min of slow wave sleep (stages 3+4) and percentage SWS.

There was no significant correlation found between body weight and, total sleep time, total min slow wave sleep or percentage SWS nor was there any significant correlation between total sleep time and total min of slow wave sleep or percentage slow wave sleep.

(e) Lack of correlation between REM sleep and age

Table 8.6 shows that none among the total min of REM sleep accumulated in the first 6h, in the whole

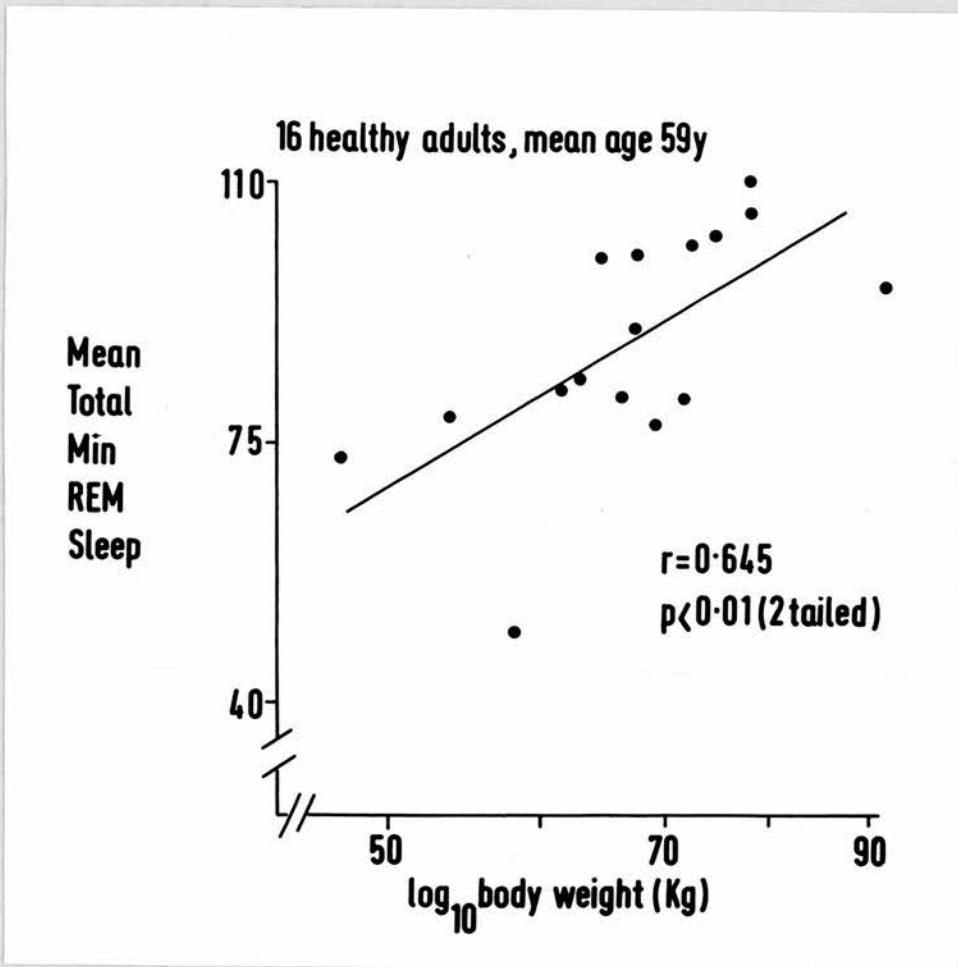


FIGURE 8.3 Correlation between mean total min of REM sleep and log body weight in 16 middle-aged subjects.

Each value of total REM sleep is the mean of 20 recorded nights.



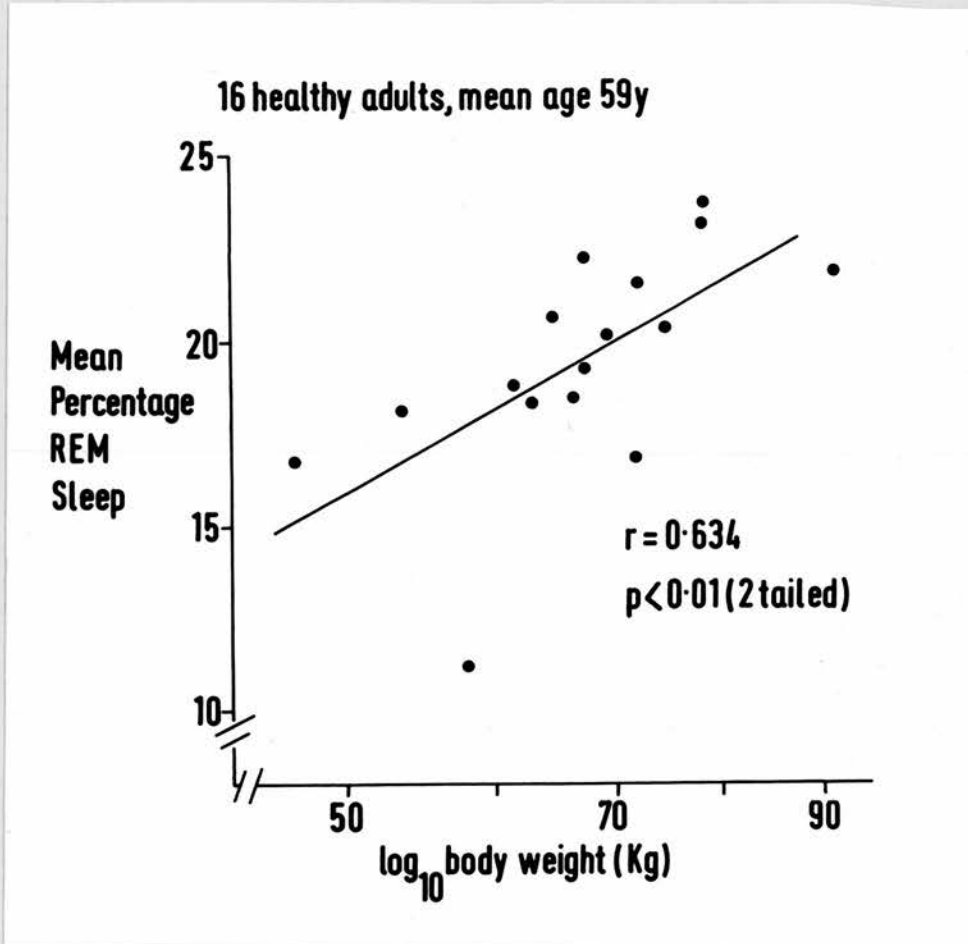


FIGURE 8.4 Correlation between the mean percentage of REM sleep and log body weight in 16 middle-aged subjects.

Each value of % REM is the mean of 20 recorded nights.

whole night, or the percentage of total sleep spent in REM sleep correlated significantly with age.

## DISCUSSION

The significance level of the correlations found between body weight and measures of REM sleep were sufficiently high ( $p < 0.01$ ) to make chance an unlikely explanation. The overall daily energy expenditure of an animal is closely related to its body weight (Kleiber, 1961) and this suggests that REM sleep may have a role associated with whole body energy balance.

It could be said that brain weight is related to body weight and that the fundamental relationship might be between brain weight and REM sleep. However, evidence from other experiments tend to suggest that it is with body weight. For example, when anorexia nervosa patients gained weight to reach their target body weight, the most striking change in their sleep pattern was an increase in REM sleep averaging about 40 min, which, even taking into account the increase in total sleep time, was still a significant rise (Lacey et al., 1975). In other experiments, compatible results were found, e.g. when ten young men were starved for four days the mean weight loss was 5.3kg and the percentage of total sleep spent in REM sleep declined by an average of 5.33 per cent (MacFadyen et al., 1973) and when three hyperthyroid patients gained weight as they became euthyroid, the amount of time they spent in REM sleep increased (Dunleavy et al., 1974).



These three reports suggest that changes in body weight are associated with parallel changes in the amount of time spent in REM sleep and so give support to my proposition, that it is with body weight that the amount of REM sleep is associated, for it is highly unlikely that brain weight was altered to any appreciable extent in the above studies. It may be that there is some other explanation for the changes in REM sleep associated with alteration in body weight due to both being mutually dependent on a third factor. A likely candidate would seem to be some aspect of the diet, either its quantity or composition.

In rats the amount of REM sleep during a 12h period including daytime sleep (when <sup>the</sup> rats accumulated most of their sleep in the 24h) was found to be inversely correlated with the quantity of food they ate in the following 12h including the night-time (when <sup>the</sup> rats eat most of their food), which suggests that relatively small day-to-day variations in the amount of REM sleep may be associated with the day-to-day differences in food intake (Siegel, 1975). In another study Dement et al. (1967) reported that cats deprived of REM sleep ate voraciously, again linking REM sleep with food intake. Normally body weight changes are related to alterations in food intake and so this could be a possible link between/

between body weight and REM sleep. In the 'set-point' theory of body weight maintenance (Powley and Keesey, 1970; Keesey et al., 1976) it is proposed that for any individual there is a pre-set level of body weight, deviations from which are monitored by the lateral hypothalamus and rectified by the appropriate alterations in appetite. It is tempting to speculate that some process involved with REM sleep is linked to a hypothalamic feeding control system for maintaining body weight. Obviously, in humans, food intake is not exclusively dependent on some internal cue and can be altered by many external factors. However, an internal regulator of body weight must surely exist to explain the extraordinary accuracy in maintaining body weight, considering the quantity of food we consume over the years.

Kleiber (1961) reported that log body weight was highly correlated with log daily metabolic rate (total calories/24h) over a number of species and I found that log body weight was correlated with total min and percentage of REM sleep. This suggests that REM sleep is related to daily energy expenditure. A large proportion of energy expenditure, even at rest about 40%, is attributable to muscle metabolism (Andres et al., 1956). A characteristic feature of REM sleep is the loss of muscle/

muscle tone, and hence a reduction in oxidative metabolism and thus a lower rate of degradation (including that of amino acids). It could be that this heretofore unexplained feature of REM sleep is a device to compensate for the relatively large energy expenditure of muscle during daytime activity.

Williams et al. (1974) presented normal data for all the usual measures of sleep and wakefulness in humans across all ages from infancy to old age. However, looking at their mean REM sleep data for the age group in which my subjects fall, I found no indication of higher amounts of REM sleep in middle-aged men compared with middle-aged women. I had thought that men would, on average, be heavier than women, but, on closer inspection of their methods, it appears that after a single adaptation night, only one sleep recording was made on each subject and that recordings only lasted about 7h. A possible explanation for the lack of difference in amount of REM sleep between the sexes in their work could be that the number of recordings that were made on each subject was insufficient to get a measure of his/her average quota of REM sleep over a sequence of nights.

To/



To conclude, I report a significant correlation between body weight and the average quota of REM sleep over a sequence of nights. This was true of the mean of each of the four blocks of five consecutive nights and the mean of the total 20 nights recorded.

I proposed that because of the high correlation between body weight and daily metabolism (total calcs/24h) reported by Kleiber (1961), a relationship between the mean amount of REM sleep and daily metabolism may exist, which in turn suggests that REM sleep may have a role in body maintenance. This of course, does not exclude other functions for REM sleep, which must exist to account for such things as the high quotas of REM sleep recorded in babies at a time when the nervous system is rapidly maturing and the large increase in REM sleep following poisoning by CNS drugs. Neither of which can be explained by a bodyweight-REM sleep relationship.

TABLE 8.1. BODY WEIGHT AND REM SLEEP

Mean body weights (lb) of each of 16 subjects. Each subject weighed eight times over 13 weeks. Weight in lb converted to kg. using conversion factor: 1 lb = 0.454 kg. (Raw data in Table 5.19).

Subjects	Sex	Mean body weight	
		lb $\pm$ S.D.	kg.
MS	F	103.69 $\pm$ 1.36	47.08
JR	F	118.56 $\pm$ 0.92	53.83
MT	F	128.19 $\pm$ 1.41	58.20
RMcD	F	135.75 $\pm$ 0.76	61.63
FW	F	139.78 $\pm$ 0.69	63.46
RR	F	142.50 $\pm$ 0.92	64.70
MW	F	146.19 $\pm$ 1.52	66.37
AH	F	148.16 $\pm$ 1.03	67.27
WH	M	148.28 $\pm$ 1.21	67.32
MC	M	152.53 $\pm$ 2.26	69.25
FC	F	157.81 $\pm$ 0.95	71.65
GH	F	159.34 $\pm$ 2.46	72.34
GJ	M	163.91 $\pm$ 0.79	74.42
AW	M	170.84 $\pm$ 0.64	77.56
KB	M	171.53 $\pm$ 1.88	77.88
JG	M	201.84 $\pm$ 1.29	91.64

TABLE 8.2. BODY WEIGHT AND REM SLEEP.

Correlations between mean body weight, mean total min of REM sleep, mean percentage of total sleep time spent in REM sleep, mean total min of REM sleep in the first 6h of sleep and mean total min asleep.

Each value for each of 16 subjects is the mean of 20 nights.

Subjects	Mean Body wt(kg)	Total min REM sleep	Percentage REM sleep	Min REM in 1st 6h sleep	Total Sleep time
MS	47.08	72.9	16.8	52.1	434.0
JR	53.83	78.5	18.1	59.5	434.9
MT	58.20	49.5	11.2	32.7	444.1
RMCD	61.63	82.4	18.8	58.9	438.9
FW	63.46	83.6	18.4	57.7	453.9
RR	64.70	100.3	20.7	70.1	485.4
MW	66.37	82.3	18.5	58.2	444.2
AH	67.27	91.6	19.3	55.1	473.7
WH	67.32	100.5	22.3	72.4	449.8
MC	69.25	77.8	20.2	68.0	384.7
FC	71.65	81.3	16.9	52.5	480.7
GH	72.34	101.7	21.6	65.8	472.0
GJ	74.42	102.5	20.4	69.8	502.5
AW	77.56	110.4	23.2	67.9	475.0
KB	77.88	105.8	23.8	73.2	445.0
JG	91.64	96.1	21.8	77.9	441.7

Correlation coefficients (r); df = 14 (2-tailed).

	Total min REM sleep	Percentage REM sleep	Min REM in 1st 6h sleep	Total sleep time
Body weight	0.633 p<0.01	0.631 p<0.01	0.651 p<0.01	0.232 (n.s.)
Total sleep time	0.481 p<0.05 (1-tailed)	0.142 (n.s.)	0.065 (n.s.)	-



TABLE 8.3. BODY WEIGHT AND REM SLEEP.

Correlations between mean body weight and the mean total min of REM sleep recorded when subjects had taken each of the four bedtime treatments. Each value for each of 16 subjects is the mean of the 5 nights recorded while on the treatment.

Subjects	Mean Body (kg)	Mean total minutes of REM sleep			
		Capsules	Flavoured Drink	Milk	Horlicks
MS	47.08	86.0	82.6	57.2	65.8
JR	53.83	76.1	70.8	91.2	75.8
MT	58.20	50.5	49.6	48.9	48.9
RMCD	61.63	82.7	69.2	97.1	80.4
FW	63.46	96.2	74.9	81.3	93.8
RR	64.70	109.1	77.9	106.4	110.0
MW	66.37	96.9	85.4	74.4	72.6
AH	67.27	85.3	99.7	93.4	87.9
WH	67.32	94.8	100.9	111.9	94.5
MC	67.25	83.7	72.7	80.1	74.8
FC	71.65	80.4	80.0	91.9	73.0
GH	72.34	97.2	105.4	97.9	106.2
GJ	74.42	103.4	104.2	96.9	105.6
AW	77.56	118.9	114.8	107.5	100.4
KB	77.88	123.9	95.1	106.2	98.1
JG	91.64	96.1	92.3	100.9	95.2

Correlation coefficients (r); df = 14 (2-tailed)

	Mean total min REM sleep on:			
	Capsules	Flavoured drink	Milk	Horlicks
Mean body weight	0.530	0.559	0.600	0.562
	p<0.05	p<0.05	p<0.02	p<0.05

TABLE 8.4. BODY WEIGHT AND REM SLEEP

Correlations between  $\log_{10}$  body weight (kg) of 16 subjects and their mean total min of REM sleep and the mean percentage of total sleep time spent in REM sleep averaged over 20 recorded nights.

Subjects	$\log_{10}$ Body weight	Total min REM sleep	Percentage REM sleep
MS	1.6728	72.9	16.8
JR	1.7310	78.5	18.1
MT	1.7649	49.5	11.2
RMcD	1.7898	82.4	18.8
FW	1.8025	83.6	18.4
RR	1.8109	100.3	20.7
MW	1.8220	82.3	18.5
AH	1.8278	91.6	19.3
WH	1.8281	100.5	22.3
MC	1.8404	77.8	20.2
FC	1.8552	81.3	16.9
GH	1.8594	101.7	21.6
GJ	1.8717	102.5	20.4
AW	1.8896	110.4	23.2
KB	1.8914	105.8	23.8
JG	1.9621	96.1	21.8

Correlation coefficients (r); df = 14 (2-tailed)

	Total min REM sleep	Percentage REM sleep
$\log_{10}$ body weight	0.645	0.634
	$p < 0.01$	$p < 0.01$



TABLE 8.5. BODY WEIGHT AND REM SLEEP.

Correlations between mean body weights of 16 subjects and their mean total time asleep, mean total min slow wave sleep (SWS) and percentage of total sleep time spent in SWS averaged over 20 nights.

Subjects	Mean body weight (kg)	Total sleep time (min )	Total min SWS	Percentage SWS
MS	47.08	434.0	37.7	8.7
JR	53.83	434.9	61.5	14.1
MT	58.20	444.1	106.8	24.1
RMCD	61.63	438.9	84.3	19.2
FW	63.46	453.9	34.1	7.5
RR	64.70	485.4	39.5	8.1
MW	66.37	444.2	85.6	19.3
AH	67.27	473.7	68.6	14.5
WH	67.32	449.8	66.6	14.8
MC	69.25	384.7	14.3	3.7
FC	71.65	480.7	84.4	17.6
GH	72.34	472.0	82.2	17.4
GJ	74.42	502.5	69.0	13.7
AW	77.56	475.0	79.8	16.8
KB	77.88	445.0	81.2	18.3
JG	91.64	441.7	77.9	17.6

Correlation coefficients (r); df = 14 (2-tailed)

	Total sleep time	Total min SWS	Percentage SWS
Body weight	0.232 (n.s.)	0.264 (n.s.)	0.224 (n.s.)
Total sleep time	-	0.352 (n.s.)	0.227 (n.s.)



TABLE 8.6. BODY WEIGHT AND REM SLEEP

Lack of significant correlation with age in 16 subjects among mean total min REM sleep, mean min REM sleep accumulated in the first 6h of sleep or the percentage of total sleep time spent in REM sleep, each averaged over 20 recorded nights.

Subjects	Age (years)	Total min REM sleep	Min REM in 1st 6h sleep	Percentage REM sleep
MS	59	72.9	52.1	16.8
JR	62	78.5	59.5	18.1
MT	50	49.5	32.7	11.2
RMCD	64	82.4	58.9	18.8
FW	67	83.6	57.7	18.4
RR	58	100.3	70.1	20.7
MW	52	82.3	58.2	18.5
AH	62	91.6	55.1	19.3
WH	54	100.5	72.4	22.3
MC	60	77.8	68.0	20.2
FC	62	81.3	52.5	16.9
GH	58	101.7	65.8	21.6
GJ	55	102.5	69.8	20.4
AW	55	110.4	67.9	23.2
KB	62	105.8	73.2	23.8
JG	57	96.1	77.9	21.8

Correlation coefficients (r); df = 14 (2-tailed)

	Total min REM sleep	Min REM in 1st 6h sleep	Percentage REM sleep
Age	-0.334 (n.s.)	-0.332 (n.s.)	-0.289 (n.s.)

CHAPTER 9

NO SIGNIFICANT CORRELATION BETWEEN I.Q. AND THE AMOUNT  
OF REM SLEEP

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CHAPTER 9

SUMMARY

The same 16 subjects, whose average quota of REM sleep correlated highly with body weight, were ranked 1-16 according to their performance on tests designed to measure intelligence. No significant rank correlations were found between I.Q. and the mean amounts of REM sleep in the whole night or the percentage of sleep time spent in REM sleep.



## INTRODUCTION

In the previous Chapter I reported a highly significant correlation between body weight and the mean amount of REM sleep. A number of investigations have indicated a relationship between intelligence quotient (IQ) and the amount of REM sleep. Petre-Quadens and Jouvet (1966) found that mental retardates had less REM sleep than normal. Feinberg et al. (1969) reported a significant correlation between the percentage of total sleep time spent in REM sleep and IQ, in 32 adult mental retardates. Another study in mongoloids, found that the reduction of REM sleep was greater in the severely retarded group than in a less retarded group (Castaldo, 1969). Castaldo and Krynicki (1973) found a positive correlation between the amount of REM sleep and IQ in retardates. The same authors later reported (Castaldo and Krynicki, 1974) a positive correlation between min of stage REM and IQ and a negative correlation between REM cycle length and IQ.

However, it has long been recognized that physical growth and mental development are connected. At the beginning of this century, Goddard (1912) reported that both body height and weight were less throughout life in mentally retarded patients than age-matched normals and that the impairment of physical growth was related to the severity of the mental retardation. More recently/

recently it has been shown that the degree of mental retardation correlates with the decrement in height and weight in children (Cully and Jolly, 1963) and in children and adults (Mosier et al., 1965).

In view of the apparent relationship between REM sleep and IQ found by Feinberg et al. (1969) in adult mental retardates, I decided to measure the performance, on IQ tests, of the 16 subjects whose body weights correlated so highly with the amounts of REM sleep recorded. In addition, I used the many tables of data given by Mosier et al. (1965) to investigate the relationship between body weight and IQ in adult mental retardates.

## METHODS

### (a) Performance measured on psychological tests

The 16 subjects, who had taken part in the study of the four bedtime treatments described in Chapter 5, were invited to come to our laboratory for an hour-long session of psychometric tests. This invitation came about a year after the sleep study and so their mean age was 60y. Ten of the subjects came at 1100h on one Sunday and the other six the following Sunday. The day of the week, the time of the day and order of tests were identical for both groups.

In consultation with a clinical psychologist, Mr. D. Peck in Edinburgh University Department of Psychiatry, it was decided to try and test both verbal and non-verbal skills. The intention was to rank subjects in order of performance on the type of tests used to measure IQ. Two standard tests were selected. One was to measure vocabulary and comprised words numbered 12 to 44 of the Mill-Hill (Senior) Set A list of 44 words (Raven, 1958) preceded by the first six words on the WAIS (Wechsler Adult Intelligence Scale Wechsler, 1955). An additional word plus an acceptable definition was included at the beginning of the list as an example of what was required (Figure 9.1).

The/



WAIS AND MILLHILL SCALE (SENIOR)

NAME: \_\_\_\_\_

INSTRUCTIONS: Please write down in a few words the meaning of each of the following words. The first word has been done for you as an example.

1. CONTINUE      Go on \_\_\_\_\_
2. BED \_\_\_\_\_
3. SHIP \_\_\_\_\_
4. PENNY \_\_\_\_\_
5. WINTER \_\_\_\_\_
6. REPAIR \_\_\_\_\_
7. BREAKFAST \_\_\_\_\_
8. STARTLE \_\_\_\_\_
9. PERFUME \_\_\_\_\_
10. MALARIA \_\_\_\_\_
11. MINGLE \_\_\_\_\_
12. FASCINATED \_\_\_\_\_
13. BRAG \_\_\_\_\_
14. PROSPER \_\_\_\_\_
15. ANONYMOUS \_\_\_\_\_
16. VERIFY \_\_\_\_\_
17. RUSE \_\_\_\_\_
18. FORMIDABLE \_\_\_\_\_
19. IMMERSE \_\_\_\_\_
20. DOCILE \_\_\_\_\_
21. VIRILE \_\_\_\_\_
22. SULTRY \_\_\_\_\_
23. STANCE \_\_\_\_\_
24. EFFACE \_\_\_\_\_
25. SENSUAL \_\_\_\_\_
26. CONSTRUE \_\_\_\_\_
27. CONCILIATE \_\_\_\_\_
28. GARRULOUS \_\_\_\_\_
29. LATENT \_\_\_\_\_
30. OBDURATE \_\_\_\_\_
31. CRITERION \_\_\_\_\_
32. PALLIATE \_\_\_\_\_
33. ADULATE \_\_\_\_\_
34. FELICITOUS \_\_\_\_\_
35. AMBIT \_\_\_\_\_
36. RECONDITE \_\_\_\_\_
37. CACHINNATION \_\_\_\_\_
38. EXIGUOUS \_\_\_\_\_
39. PUTATIVE \_\_\_\_\_
40. MANUMIT \_\_\_\_\_

FIGURE 9.1 MILLHILL VOCABULARY TEST. The figure is a photographically reduced ( $\times 0.83$ ) copy of the vocabulary test given to the 16 middle-aged subjects.

The first six 'easy' words from the WAIS test were included at the beginning of the test to give the subjects practice in composing meanings of words, and the answers to those were not included in the assessments. Subjects were allowed 30 min to complete this assignment.

The aim of this test was to measure subjects' "present recall of acquired information and ability for verbal communication".

The other test was Raven's Matrices test (Raven, 1960), where subjects are asked to match one of six (or eight) alternative pieces of pattern to a space in a large pattern. Subjects were allowed 30 min on this test. The test was designed to measure a person's present capacity for intellectual activity and rational judgement.

The combination of the vocabulary test and the Matrices test has apparently proved reliable in assessing intelligence (Raven, 1958).

The vocabulary test was supposed to be given orally to a subject and the subject's answers written down verbatim by the investigator. It was, however, decided to give the test as a written paper because of the time required to test the 16 subjects individually, for most of them could only attend the laboratory in the/

the later evening or on a Sunday, but perhaps the more important reason was that I know all the subjects so well that I felt some of them might have been embarrassed if they felt they performed poorly on the test.

The two groups were given the tests in the same order, first the Raven's Matrices test, then the vocabulary test, and the identical instructions were read to them prior to each test. Figure 9.2 is a copy of the information read to the subjects before the Matrices test and the instructions listed at the top of the vocabulary test (Figure 9.1) were read aloud by the investigator and in addition they were told that they should not be worried if they failed to define all the words as this was a very difficult test. There was a five-minute break between the tests.

Both tests were scored by the psychologist who knew none of the subjects. He scored the subject's definitions of words 7 to 40 on the vocabulary list on a three point scale viz. 0, 1 and 2. Marks were awarded in accordance with the standards listed in the instruction manual accompanying the test (Raven, 1958). Each subject's total score on the test, taking into account his/her age, was interpolated into an estimate of IQ using the standard conversion tables.

The/



### RAVEN'S PROGRESSIVE MATRICES

#### Instructions

If you open the book in front of you at page A1, you will see a large patterned rectangle with a vacant slot in one corner. Beneath the rectangle, there are 6 figures, one of which will fit into the vacant slot to complete the pattern of the rectangle. Each figure is the same shape as the slot, but only the one with the matching pattern is the missing piece. In this case, the missing piece is figure 4.

If you look on the answer-sheet you will find the answer to A1 has already been done.

In a minute, we would like you to turn over the page and work through the book, carefully selecting the figure, which represents the missing piece from the pattern on the rectangle.

Working down each column of the answer-sheet as you go through the book, write down the number of the figure you choose as the missing piece, for each of the pictures.

You will have half-an-hour to do as many as you can. Do not worry if you cannot finish - it does not matter. Some of them are quite hard. If you come to one which you can't do don't spend too much time over it, go on and try the next one. But, always make sure you write your answer in the space labelled with the same letter and number as the page you are doing

Does any one have any questions?

FIGURE 9.2 Instructions read to subjects before they attempted the Raven's progressive matrices.

The answers to the Raven's matrices test were marked as correct (1 point) or wrong (0 points) and the score converted into an IQ using the standard tables of this test and taking into account subject's age (Raven, 1960).

Spearman's rank correlation test (Siegel, 1956) was used to test the significance of any correlation between the IQ of subjects and the amount of REM sleep recorded and their body weights.

(b) Calculations using the data of Mosier et al.

Mosier et al. (1965) reported the mean body weights and mean heights of a very large number of mentally retarded patients. They sub-divided patients into the two sexes, three IQ ranges and 21 age groups (from a group comprising those less than 30 months old to one of those over 40 years old. I selected out the body weight data from the six highest age groups for both the male and female adults (over 16y). This data was collected from 1253 patients. For every age group and for either sex a mean body weight was presented for each IQ band so there were 12 mean body weights for those adults with IQs below 20. 12 age-matched mean body weights for those with IQs of 20 or above but below 50 and a matched set of mean body weights for/

for those with IQs of 50 or above. I calculated the mean body weight for each IQ band. I used Friedman's analysis of variance by ranks (Siegel, 1956) to test whether the lowest IQ band was associated with the lowest mean body weights and the highest IQ band with the highest mean body weights.



## RESULTS

(a) Subjects ranked in order of their performance on the IQ tests.

I will use the term IQ for brevity but really mean their relative performance on these psychological tests.

Table 9.1 lists the IQs estimated from the two tests and the mean IQ for each subject.

It was never intended to use the numerical values of IQs but only to rank the subjects in order of performance on the two IQ tests, and so the rank order listed in the Table is what was used in the statistical testing of the results. Unfortunately, the range of mean IQ was rather narrow, 93 to approximately 125.

(b) Spearman's rank correlations ( $r_s$ ) - (Table 9.2)

In this group of middle-aged subjects, the rank order of IQ was not significantly correlated with the rank order of mean percentage of total sleep spent in REM sleep or mean total min of REM sleep recorded. Nor was IQ significantly correlated with body weight whereas body weight was highly correlated with both percentage REM sleep:  $r_s = 0.774$ ,  $p < 0.001$  (2-tailed) and mean min of REM sleep:  $r_s = 0.721$ ,  $p < 0.005$  (2-tailed).

(c) Analysis of the results of Mosier et al.

The mean weights of each age group were subdivided into the three IQ bands. The overall mean body weight for each IQ band showed that the mean weight for the highest IQ band was greater than the intermediate IQ band, which in turn was higher than the lowest IQ band. Analysis of variance by ranks, using each age group's mean body weights for each IQ band, revealed a highly significant association between IQ and body weight  $\chi^2_r = 20.7$   $p < 0.001$  (Figure 9.3).

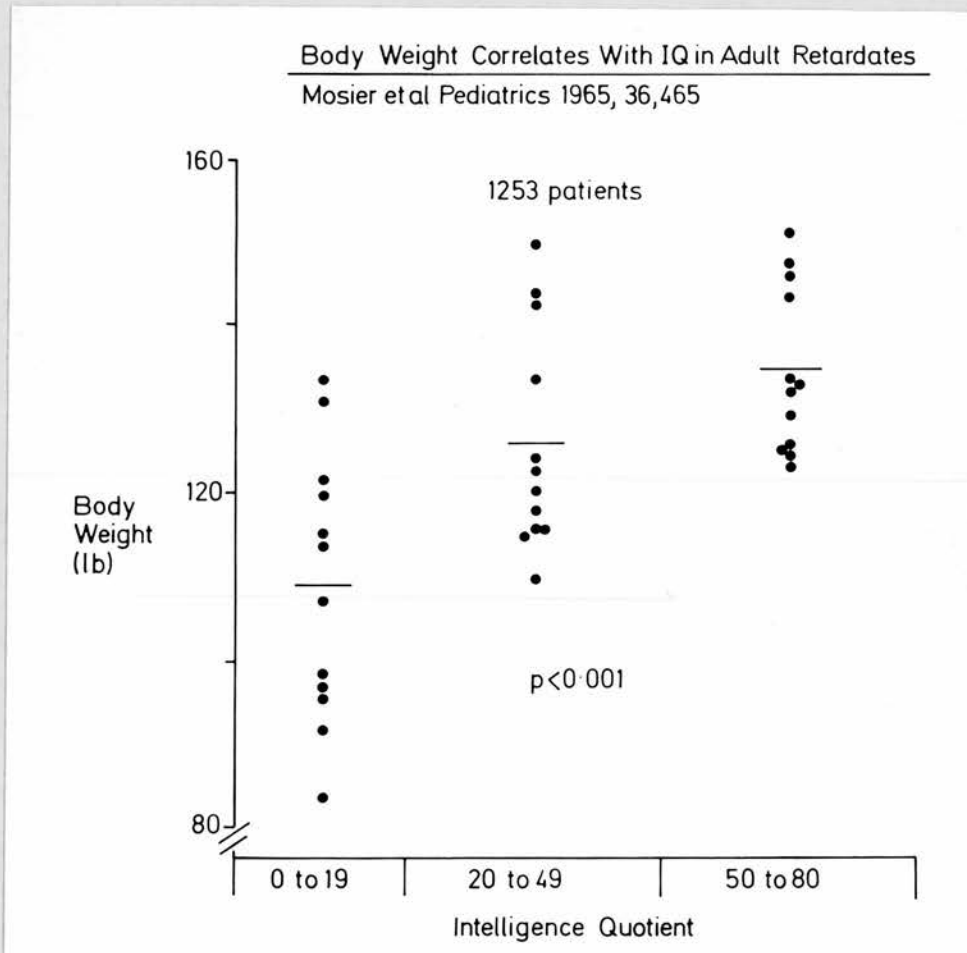


FIGURE 9.3 Correlation between I.Q. and body weight in adult mental retardates.

Each point on the graph is the mean body weight of one age group of adult mental retardates in the particular I.Q. band. Men and women were treated separately. For statistical purposes the mean body weights of each age group (and either sex) in the three I.Q. bands were compared.



## DISCUSSION

The psychological testing of the 16 subjects showed that they differed in their ability to perform the tests and could be separated into a rank order. However the spread of estimated IQ was rather narrow and so the lack of relationship found between performance on these tests and REM sleep cannot be extrapolated to other groups. Nevertheless, the correlations found between their body weights and measures of REM sleep were highly significant and this, coupled with the highly significant relationship between IQ and body weight in groups of adult mental retardates (Mosier et al., 1965) does suggest that the correlation between REM sleep and IQ in adult retardates reported by Feinberg et al. (1969) may in fact be largely attributable to the relationship of both these variables to body weight.

TABLE 9.1. LACK OF CORRELATION BETWEEN I.Q. AND REM SLEEP.

16 Subjects ranked in order of their intelligence quotient based on the I.Q.'s estimated, on:

(a) Millhill vocabulary test.

(b) Raven's matrices test.

Then the scores on (a) and (b) averaged.

Subjects	(a) Vocabulary test		(b) Raven's matrices		Mean of	
	I.Q.	Rank Order	I.Q.	Rank Order	(a) and (b) I.Q.	Rank Order
KB	126	1	104	13	115.0	7
GH	111	8	130	2	120.5	4
JG*	110	9	130+	1	125+	1
GJ	116	4.5	123	6	119.5	5
MS	112	6.5	101	14	106.5	13
JR	118	2.5	109	11.5	113.5	10
WH	109	10	109	11.5	109.0	11
FW	116	4.5	128	3	122.0	2
AW	101	14	114	9.5	107.5	12
MW	96	15.5	114	9.5	105.0	14
RR	108	11.5	126	4	117.0	6
MT	118	2.5	125	5	121.5	3
RMCD	112	6.5	117	8	114.5	8
AH	108	11.5	120	7	114.0	9
FC	102	13	83	16	92.5	16
MC	96	15.5	98	15	97.0	15

NOTE\*: This subject performed so well on the Raven's matrices test that the psychologist could not give me a value for this subject's I.Q. on that test. It was nevertheless well in excess of 130, and so this particular subject was ranked first overall.

TABLE 9.2. LACK OF CORRELATION BETWEEN I.Q. AND REM SLEEP.

16 Subjects ranked in order of their mean body weight, assessed intelligence quotient (I.Q.) and mean percentage of total sleep spent in REM sleep and the mean total min of REM sleep (the latter two averaged over 20 recorded nights).

Variables ranked 1 to 16

Subjects	Body wt. 1 = heaviest	I.Q. 1 = highest	% REM 1 = highest	Total REM 1 = highest
MS	16	13	15	15
JR	15	10	13	13
MT	14	3	16	16
RMCD	13	8	10	10
FW	12	2	12	9
RR	11	6	6	6
MW	10	14	11	11
AH	9	9	9	8
WH	8	11	3	5
MC	7	15	8	14
FC	6	16	14	12
GH	5	4	5	4
GJ	4	5	7	3
AW	3	12	2	1
KB	2	7	1	2
JG	1	1	4	7

Spearman's rank correlations ( $r_s$ ):  $df = 14$  (2-tailed).

	Rank order of:		
	I.Q.	Percentage REM sleep	Total min REM sleep
Body weight	0.12 (n.s.)	0.774, $p < 0.001$	0.721, $p < 0.005$
I.Q.	-	0.174 (n.s.)	0.288 (n.s.)



CHAPTER 10

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## CHAPTER 10

### SUMMARY

In a group of 16 middle-aged subjects it was found that the more obese individuals had longer NREM-REM sleep cycles than those of normal body weight, and the under-weight subjects had shorter sleep cycles. Also the more obese an individual was the longer he/she slept each night and conversely the more underweight subjects slept, on average, less than the subjects of normal weight.

## INTRODUCTION

NREM-REM sleep cycles are a feature of normal nocturnal sleep. A cycle is made up from a period of NREM sleep plus an adjacent period of REM sleep and each cycle lasts, on average, around 100 min in the human adult.

These sleep cycles are thought to be the manifestation of an ultradian rhythm present throughout the 24h (Kleitman, 1963) and a daytime rhythm of similar periodicity has been reported on a number of different measures. For example, many years ago Wada (1922) described how gastric contractions recurred every 90-100 min during the waking period. Oral activity has also been shown to have a similar periodicity in waking man. Friedman and Fisher (1967) studied the oral habits of normal individuals, through a one-way window, over a period of hours. They found that all subjects displayed rhythmicity in their oral behaviour and the mean periodicity was 96 min. Friedman (1972) also studied obese patients under a similar regime. He found they had a marked and regular pattern of oral activity but with a higher frequency than in the normal subjects (mean interval of 78.8 min). The cycle length was found to be inversely correlated with the degree of obesity. In both these studies the different items available/



available for oral activity were graded according to psychoanalytical concepts, so that milk a supposedly primal food scored more points than, say, a doughnut.

A better controlled study, using an unweighted scoring system for any feeding or drinking behaviour, confirmed that in a neutral environment cyclic oral activity occurred at about 97 min intervals in adults (Oswald et al., 1970).

Other studies have shown similar rhythmicity in physiological measures such as heart rate (Orr and Hoffman, 1974; Orr et al., 1974) in performance on various psychometric tests, for example, on complex signal detection tasks (Orr et al., 1974; Globus et al., 1971), in day-dreaming (Kripke, 1974) and cortical arousal (Lavie et al., 1975).

Studies have suggested that the cyclical appearance of REM sleep (REM cycles) is related to metabolic rate (cal/kg) in such a way that higher metabolic rate is associated with shorter REM cycle lengths. This has been found in studies across species (Hartmann, 1968; Zepelin and Rechtschaffen, 1974) and within a species, rats, (Weiss and Roldan, 1964). From this one might predict that sleep cycle length would be related to body weight, because body weight is inversely related to metabolic rate (cal/kg).

I/

I set out to investigate this apparent relationship between metabolic rate and sleep cycle duration and to see if the degree of overweight (or underweight) was related to the length of sleep cycles. The latter question was raised by Friedman's report (1972) that the daytime oral activity rhythm of obese patients displayed a higher frequency than was found in normals.

## METHODS

### (a) Electrophysiological recordings of sleep

Each subject had his/her sleep recorded on 20 nights as described in Chapter 4. For the purposes of this study the mean total min asleep, mean total min of slow wave sleep, mean total min of REM sleep and the mean NREM-REM sleep cycle length were calculated for each subject over the 20 nights.

The mean length of the first three NREM-REM cycles of sleep was calculated as follows. Each cycle started with a period of NREM sleep and the first cycle commenced with the onset of sleep (first appearance of stage 2). The first cycle comprised all the NREM sleep stages occurring after this first stage 2 plus the following REM period. The end of the first cycle and the beginning of the second was marked by the first appearance of stage 2 after completion of the period of REM sleep. The period of REM sleep was judged complete when the amount of NREM sleep following the last page scored as REM sleep exceeded 15 min.

Only NREM-REM sleep cycles containing one minute or less of wakefulness were included in the calculations, because Březinová (1974b) found that sleep cycles broken by wakefulness were longer than the corresponding intact cycles.

The/



The mean lengths of a subject's first, second and third sleep cycles were calculated, using data from intact cycles only (as defined above). Thereafter the mean lengths of the first, second and third sleep cycles were averaged to give a mean value for each subject's first three sleep cycles. This method of calculating the mean sleep cycle length (of the first three cycles) was chosen because the first NREM-REM cycle in adults is on average shorter than the second and third cycles (Feinberg, 1974; Březinová, 1974b). If a person had, on average, many broken cycles later in the night and few broken first cycles, then the above method of calculation would allow an equal contribution to the mean from each of the three mean cycle lengths.

(b) Measurement of body weight

Subjects were weighed on eight occasions and the mean taken (as described in the Methods section of the previous Chapter).

(c) Measurement of standing height

The standing height of each subject was measured (Figure 10.1), without shoes, using a wall-mounted stadiometer (designed by Tanner and Whitehouse, and marketed by Harpenden) and employing the recommended technique/



FIGURE 10.1 The Harpenden Stadiometer in operation.



technique viz. the subject is asked to stand with his or her heels, bottom, shoulders and back of the head touching the vertical surface of the stadiometer, with arms hanging loosely at the sides of the body. The investigator then rests the sliding board on the top of the head and adds a weight on top of the board to ensure contact between the under surface of the board and the top of the head. The investigator then adjusts the position of the subject's head so that an imaginary line between the outer corner of the subject's eye and the top of the ear is judged to be horizontal. Thereafter the investigator asks the subject to breathe in and then stretches the subject to his/her maximum height by lifting upwards while pressing on the mastoid bones with the tips of the fingers. Subjects were asked not to lift up their heels and, in practice, it was easy to detect this, as subjects feel 'too elastic' when this happens. On expiration the subject is held in the 'stretched' position and his/her height read off a counter calibrated in mm.

(d) Calculation of the ideal body weight for each subject.

The heights of subjects, measured as above, were converted into feet and inches and the Metropolitan Life Insurance Company tables (1960) consulted to determine/



determine the ideal weight for each subject. Before consulting the tables I rated subjects' frame sizes into small, medium or large. All except two subjects were considered to be of medium build and the two exceptions, i.e. MS and JG, were very obviously of small and large frame respectively.

The standard tables, referred to above, list a range of weights for each frame size and the mean of each range of weights in the table was used in the calculations. The tables include an allowance for a 2" heel on women's and 1" heel on men's heights and these allowances were added to the heights of my subjects as they had been measured in their stocking-soles. The mean ideal body weight for each subject was subtracted from his/her mean measured weight and the positive or negative deviation from the ideal expressed as a percentage of ideal, i.e.

$$\text{Percentage deviation from ideal body weight} = \frac{\text{mean measured BW} - \text{mean ideal BW}}{\text{ideal body weight}} \times 100$$

(e) Calculation of Quetelet's index

Quetelet's index of obesity  $\frac{W}{H^2}$  (where W is the body weight and H the standing height of the subject) was calculated for each subject using the mean body weight in lbs and measured height in inches (Khosla and Lowe, 1964). The value of the index was multiplied by 100.

## STATISTICS

Pearson's product-moment correlation test (Ferguson, 1959) was used to test the significance of the relationship between the various measures. In a case where significant correlations were found among three variables then partial correlation analysis was carried out (Ferguson, 1959) to ascertain what percentage of the association between one pair of variables was attributable to the third variable.

Linear regression by the method of least squares was employed to fit a straight line through data points graphically presented (Ferguson, 1959).

## RESULTS

### (a) NREM-REM sleep cycles

The mean length of the first three sleep cycles was  $105.2 \pm 12.4$  min and ranged from 82.8 min to 122.1 min over the 16 subjects (Table 10.1). The mean length of the first sleep cycle was  $102.4 \pm 21.2$  min, the second  $110.8 \pm 13.5$  min and the third cycle  $102.4 \pm 12.9$  min.

I felt justified in averaging only the first three cycles, because many of the subjects only had three complete cycles and the number of later cycles was too small.

### (b) Lack of correlation between body weight and NREM-REM cycle length.

Mean body weight was not significantly correlated with the mean length of a subject's NREM-REM cycles, where all the intact first, second and third sleep cycles had been averaged:  $r = 0.164$  (Table 10.1).

### (c) Correlations between percentage deviation from ideal body weight and the mean NREM-REM cycle length.

Table 10.2 lists the 16 subjects in order of increasing body weight paired with their measured height converted into feet and inches. The ideal body weight/



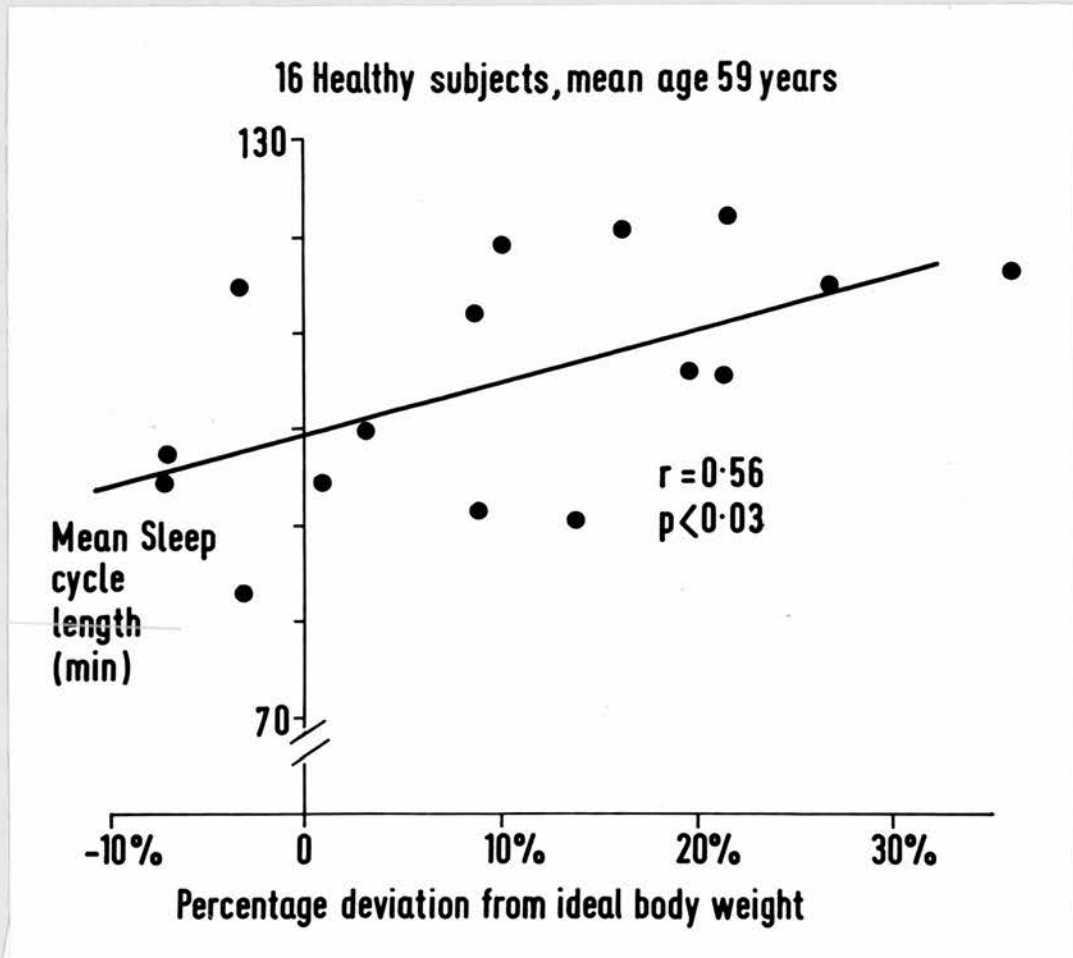


FIGURE 10.2 Correlation between the percentage deviation from ideal body weight and the mean NREM-REM sleep cycle length (averaged over the first three intact cycles). Sleep cycle data for each of the 16 middle-aged subjects collected over 20 nights.

Data in Table 10.3.

weight for each subject, taking into account their height and frame size is listed in lbs. Eleven of the subjects weighed more than their ideal body weight (from + 4 lb to + 42 lb) and only five weighed the same or less (from 0 lb to -9 lb) than their ideal body weight.

The deviations from ideal body weight were transformed into percentages of ideal body weight and the percentage deviations ranged from -7.14% to + 36.21%. The percentage deviation from ideal body weight was significantly correlated with the mean sleep cycle length:  $r = 0.563$   $p < 0.03$  (Table 10.3 and Figure 10.2)

(d) Correlation between Quetelet's index and mean NREM-REM cycle length.

The value of Quetelet's index ranged from 2.71 to  $4.25 \text{ lb inch}^{-2} \times 10^2$  over the 16 subjects. There was a significant positive correlation between the value of the index and the mean length of the first three sleep cycles:  $r = 0.498$ ,  $p < 0.05$  (Table 10.4).

(e) Correlations between mean sleep cycle length and other measures of sleep.

Mean NREM-REM sleep cycle length was significantly correlated with the mean total sleep time:  $r = 0.572$ ,  $p < 0.03$  but not with total min of REM sleep:  $r = -0.022$  or total min of slow wave sleep:  $r = 0.405$  (Table 10.3) but/

but the mean sleep cycle length was significantly correlated with the mean total min of REM sleep accumulated in the first three sleep cycles:  $r = 0.575$ ,  $p < 0.03$  (Table 10.5).

(f) Correlations with percentage deviations from ideal body weight.

The mean total time that subjects slept was positively correlated with the percentages by which their measured body weights deviated from the ideal:  $r = 0.536$ ,  $p < 0.04$  (Figure 10.3), whereas neither total min of REM sleep nor total min of slow wave sleep significantly correlated with the percentage deviation from ideal body weight (Table 10.3).

(g) Partial correlations

The mean sleep cycle length was significantly correlated with both percentage deviation from ideal body weight and the mean total sleep time. Table 10.6 shows the partial correlation ( $r_{12.3}$ ) and the product-moment correlation coefficients ( $r$ ) between pairs of these three variables. From these two correlation coefficients the percentage of the total association ( $r$ ), between two of the variables, attributable to the third variable was calculated. 57% of the association between sleep/



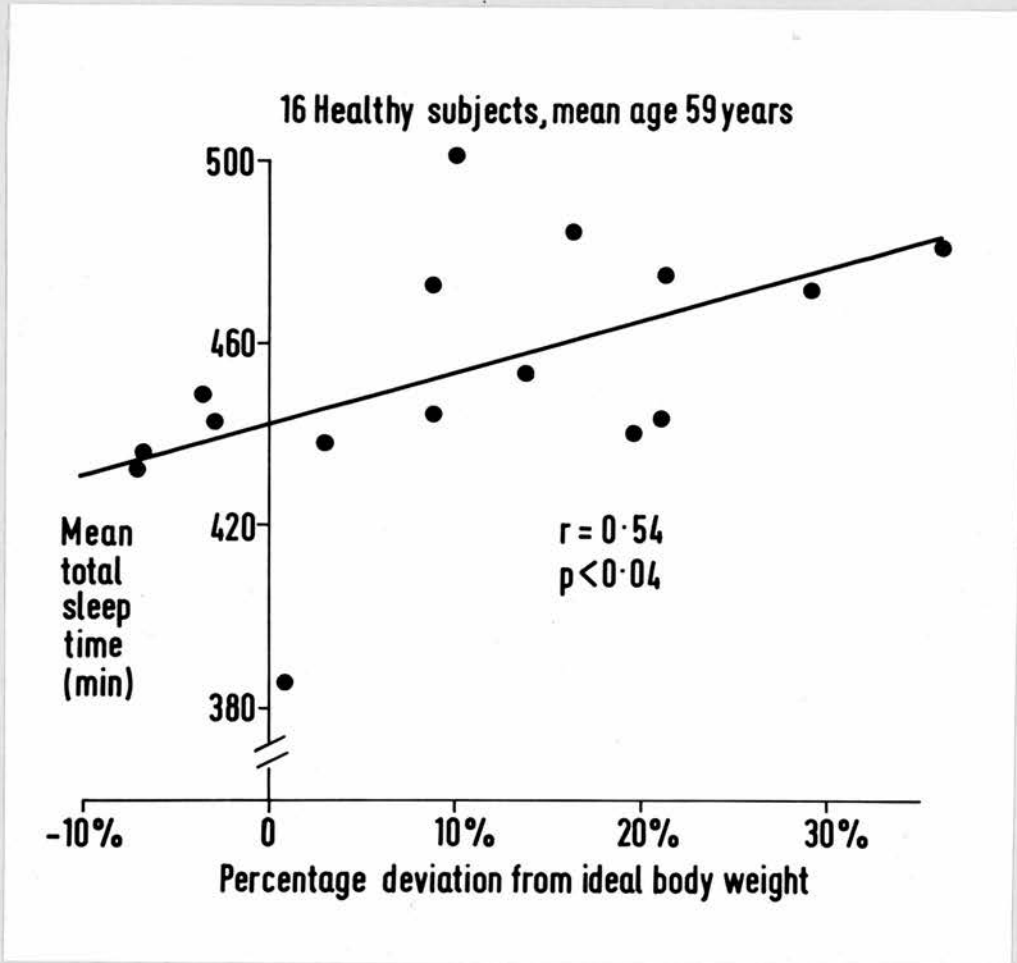


FIGURE 10.3 Correlation between the percentage deviation from ideal body weight and the mean total sleep time. Sleep data for each of the 16 middle-aged subjects collected over 20 nights.

Data in Table 10.3.

sleep cycle length and percentage deviation from ideal body weight is due to their joint association with mean total sleep time.

54% of the association between sleep cycle length and total sleep time owes to their joint association with percentage deviation from ideal body weight.

65% of the association between total sleep time and percentage deviation from ideal body weight is attributable to their common association with sleep cycle length.

## DISCUSSION

NREM-REM sleep cycles have been found, by a number of investigators, to be positively correlated with metabolic rate (Weiss and Roldan, 1964; Hartmann, 1968; Zepelin and Rechtschaffen, 1974).

Metabolic rate and body weight are inversely related, but I found no significant correlation between crude body weight and sleep cycle length. Admittedly there are a number of differences between my study and those above, all the latter were cross-species investigations, except the Weiss and Roldan study of rats and they all defined sleep cycles as the min between the onset of one period of REM sleep and the beginning of the following period of REM sleep. But it has been suggested (e.g. Hartmann, 1973; Feinberg, 1974) that the appearance of REM sleep is dependent on some process occurring during the preceding period of NREM, because NREM sleep always precedes REM sleep (except in rare pathological conditions) and so it seemed more sensible to regard a sleep cycle as a period of NREM sleep plus its following period of REM sleep. However, this is just a technical quibble as these are two ways of looking at the same rhythm and you would expect agreement between the two methods.

I/



I did find a significant correlation between the mean NREM-REM sleep cycle length and the percentage by which a person's body weight deviated from his/her ideal body weight, which suggests a connection between the degree of over-or underweight for height and the frequency of a fundamental brain rhythm.

I found that the degree of obesity was positively correlated with the length of the cycle, which is the opposite of what might be expected from Friedman's (1972) finding that the frequency of obese patients' oral activity rhythm was inversely related to the degree of obesity. Of course the question arises, are we measuring manifestations of the same fundamental rhythm? I do not think this can be answered until a study over 24h is done and the phase relationship between the oral activity rhythm and sleep cycle rhythm investigated. To expect the sleep cycle rhythm to be of a frequency similar to that of a waking rhythm implies that there is an endogenous clock controlling these different rhythms and that the cyclical appearance of REM sleep is dependent on an ultradian rhythm and not on sleep itself. Globus et al. (1969) tried to show that REM periods were the manifestation of a sleep-independent internal clock, however Brezinová (1974b) demonstrated that the composition (i.e. amounts/

amounts of wakefulness, slow wave and REM sleep) of a sleep cycle influences its duration, which suggests that this rhythm must, at least in part, be dependent on sleep and is not purely an ultradian rhythm. Evidence for this proposition is seen in the variation in sleep cycle length across the night. Globus, (1970) sees this as the result of an ultradian rhythm with a cycle duration of about 100 min interacting with the circadian sleeping-waking rhythm and resulting in frequency modulation.

Further evidence that the cyclical appearance of REM sleep is probably dependent on sleep was reported by Brezinová et al. (1975). They investigated the effect of awakening subjects for one hour, after the end of their second REM period. Thereafter subjects were allowed to fall asleep and the time until the third REM period reappeared was measured. From their results they concluded that REM periods are not locked to certain times of the 24h, for interruption of sleep by 1h of waking seemed to reset the rhythm. The third REM period did not appear at the expected time but was delayed for nearly an hour, when uninterrupted nights were compared with interrupted nights, suggesting that the timing of the appearance of a REM sleep period is dependent on the preceding non-REM sleep period.

Moses/

Moses et al. (1977) came to the same conclusion, using a different approach. They analysed the data collected from three separate studies of altered sleep-wake schedules, where subjects accumulated sleep across the 24h in a series of naps:

(a) Alternating 30 min sleep - 60 min awake for five

days (b) 60 min sleep-20 min awake for ten days

(c) 60 min sleep - 160 min awake for 40h. In all

three studies a series of uninterrupted baseline nights had been recorded to establish each subject's usual REM sleep cycle duration. The hypothesis was that if the cyclical appearance of REM sleep is sleep-dependent then the mean baseline REM sleep cycle length should not differ significantly from the average length of the interval between the onset of REM periods on the sleep/nap regimes when the wake periods are subtracted. Their hypothesis was confirmed, in other words, a certain amount of non-REM sleep and not just time must be accumulated before REM sleep reappears. The authors believe that their results show that the ultradian rhythms found in various waking activities are not an expression of the REM cycle found in sleep, but are dependent on a separate neurophysiological process. If this is the case it may explain why I found the opposite relationship between obesity and cycle length to that reported by Friedman in his oral activity experiment.

There/



There is some evidence to support the positive correlation between degree of overweight and sleep cycle length in the report by Boccalon et al. (1976) that body weight in seven obese subjects was positively correlated with REM cycle length, but this was only an abstract and no details were given. I would predict that increasing body weight among their obese subjects would be associated with increasing percentage deviation from ideal body weight, and so our results would seem to be compatible.

It would be interesting to see if mean sleep cycle length is static or if its frequency changes as body weight moves above or below the ideal body weight for an individual. The former would suggest that people are inherently programmed to be a certain weight and the latter that this brain rhythm is related to alterations in metabolism associated with changes in body weight.

I also found that total sleep time was positively correlated with the percentage deviation from ideal body weight, which is evidence for the popular view that fat people sleep longer. It also is consistent with the findings of Crisp et al. (1973) who reported that obese patients slept less as they lost weight and of Lacey et al. (1975) who found that anorexia nervosa/

nervosa patients slept longer as their weight was regained.

Total sleep time was also positively correlated with the mean sleep cycle duration, so the three factors: total sleep time, sleep cycle length and percentage deviation from ideal body weight were all found to be associated. Partial correlation analysis showed that the correlation found between any two of these variables was not independent of the third. Of the three pairings of variables, the influence of sleep cycle length on the correlation between total sleep time and percentage deviation from ideal body weight was marginally greater than the influence of either of the other two on correlations with sleep cycle duration. The correlations between these three variables may of course be due to all of them being associated with a fourth variable.

TABLE 10.1. SLEEP CYCLES AND BODY WEIGHT.

Lack of any significant correlation between mean body weight and the mean NREM-REM cycle length (the mean lengths of the first three intact NREM-REM cycles were averaged). NREM-REM cycle data collected over 20 nights for each of the 16 subjects.

Subjects	Mean NREM-REM cycle length						Mean of 1st 3 cycles min.	Mean Body wt. (kg)
	1st cycle min.	n*	2nd cycle min.	n*	3rd cycle min.	n*		
MS	89.4	(18)	94.6	(18)	100.7	(16)	94.9	47.08
JR	107.9	(4)	97.7	(6)	86.6	(7)	97.4	53.83
MT	151.6	(11)	105.9	(11)	87.0	(11)	114.8	58.20
RMCD	93.0	(11)	107.6	(10)	99.8	(13)	100.1	61.63
FW	92.2	(3)	88.3	(8)	90.8	(9)	90.4	63.46
RR	101.4	(8)	129.1	(14)	131.2	(11)	120.6	64.70
MW	125.9	(12)	125.7	(10)	114.8	(4)	122.1	66.37
AH	113.9	(5)	110.1	(17)	112.2	(14)	112.1	67.27
WH	71.4	(12)	91.7	(8)	85.4	(8)	82.8	67.32
MC	71.2	(2)	103.5	(8)	107.2	(7)	94.0	69.25
FC	113.4	(14)	125.9	(10)	109.3	(13)	116.2	71.65
GH	109.0	(13)	127.9	(16)	107.1	(8)	114.9	72.34
GJ	126.6	(16)	119.6	(19)	112.4	(17)	119.5	74.42
AW	95.8	(12)	112.9	(8)	107.9	(12)	105.5	77.56
KB	80.7	(16)	108.4	(10)	86.0	(11)	91.7	77.88
JG	95.3	(17)	124.1	(20)	99.5	(12)	106.3	91.64
Mean	102.4		110.8		102.4		105.2	
+S.D.	+21.2		+13.5		+12.9		+12.4	

Correlation coefficient (r) between body weight and mean NREM-REM sleep cycles length:  $r = 0.164$ ,  $df = 14$  (n.s.)

NOTE: n\* = number of intact sleep cycles (containing 1 min or less of wakefulness) contributing to the mean.



TABLE 10.2. SLEEP CYCLES AND BODY WEIGHT.

The deviation of each subject's measured body weight, from the ideal body weight for his/her measured height. This deviation (in lbs) from the ideal was then converted into a percentage deviation from the ideal body weight.

Subjects	Mean measured body wt. (lb)	Height ft. in.	Ideal weight (lb)	Deviation (lb) from ideal body weight	% Deviation
MS	104	5' 2"	112	- 8	- 7.14
JR	119	5' 4"	128	- 9	- 7.03
MT	128	5' 5"	132	- 4	- 3.03
RMcD	136	5' 5"	132	4	3.03
FW	140	5' 3"	123	17	13.82
RR	143	5' 3"	123	20	16.26
MW	146	5' 2"	120	26	21.67
AH	148	5' 6"	136	12	8.82
WH	148	5' 9"	153	- 5	- 3.27
MC	153	5' 9"	153	0	0.0
FC	158	5' 1"	116	42	36.21
GH	159	5' 3"	123	36	29.27
GJ	164	5' 8"	149	15	10.07
AW	171	5' 6"	141	30	21.28
KB	172	5' 10"	158	14	8.86
JG	202	5' 10"	169	33	19.53

\* All subjects judged to be of medium build except,  
MS - small frame and JG - large frame.

Ideal weights calculated from Metropolitan Life  
Assurance Tables.

TABLE 10.3. SLEEP CYCLES AND BODY WEIGHT.

Correlations between the mean NREM-REM sleep cycle length (average of the mean first, second and third intact sleep cycles), percentage deviation from ideal body weight (BW), mean total sleep time, mean total min REM sleep and mean total min slow wave sleep (SWS).

All the values for the sleep measures for each of the 16 subjects are the means over 20 nights.

Subjects	Sleep cycle length (min.)	% Deviation from ideal body weight	Total sleep time (min.)	Total min. REM sleep	Total min. SWS
WH	82.8	- 3.27	449.8	100.5	66.6
FW	90.4	13.82	453.9	83.6	34.1
KB	91.7	8.86	445.0	105.8	81.2
MC	94.0	0.0	384.7	77.8	14.3
MS	94.9	- 7.14	434.0	72.9	37.7
JR	97.4	- 7.03	434.9	78.5	61.5
RMcD	100.1	3.03	438.9	82.4	84.3
AW	105.5	21.28	475.0	110.4	79.8
JG	106.3	19.53	441.7	96.1	77.9
AH	112.1	8.82	473.7	91.6	68.6
MT	114.8	- 3.03	444.1	49.5	106.8
GH	114.9	29.27	472.0	100.7	82.2
FC	116.2	36.21	480.7	81.3	84.4
GJ	119.5	10.07	502.5	102.5	69.0
RR	120.6	16.26	485.4	100.3	39.5
MW	122.1	21.67	444.2	82.3	85.6

Correlation coefficients (r) : df = 14 (2-tailed)

	% Deviation from ideal BW	Total sleep time	Total min. REM sleep	Total min. SWS
Sleep cycle length	0.563	0.572	- 0.022	0.405
	p < 0.03	p < 0.03	(n.s.)	(n.s.)
% deviation from ideal BW	-	0.536	0.417	0.293
		p < 0.04	(n.s.)	(n.s.)



TABLE 10.4. SLEEP CYCLES AND BODY WEIGHT.

Correlation between the Quetelet's index of obesity and the mean length of the first three intact NREM-REM sleep cycles. The sleep cycle data for each of 16 subjects was collected over 20 recorded nights.

$$\text{Quetelet's index} = \frac{W}{H^2} \times 100 \text{ lb inch}^{-2} \times 10^2$$

W = body wt. in lbs.; H = standing height in inches.

Subjects	Quetelet's index	Value of Quetelet's index for 'ideal' body weight	Mean sleep cycle length (min.)
MS	2.71	2.91	94.9
JR	2.91	3.13	97.9
MT	3.03	3.12	114.8
RMCD	3.22	3.12	100.1
FW	3.53	3.10	90.4
RR	3.60	3.10	120.6
MW	3.80	3.12	122.1
AH	3.40	3.12	112.1
WH	3.11	3.21	82.8
MC	3.21	3.21	94.0
FC	4.25	3.12	116.2
GH	4.01	3.10	114.9
GJ	3.55	3.22	119.5
AW	3.93	3.24	105.5
KB	3.51	3.23	91.7
JG	4.12	3.45	106.3

Correlation coefficient between Quetelet's index and NREM-REM sleep cycle length.

$$r = 0.498, \quad p < 0.05, \quad df = 14 \text{ (2-tailed)}$$



TABLE 10.5 SLEEP CYCLES AND BODY WEIGHT

Correlation between the mean total min of REM sleep accumulated in the first three NREM-REM sleep cycles and the mean sleep cycle length. Each value for each of 16 subjects is the mean over 20 recorded nights.

Subjects	Mean total min REM sleep in 1st 3 sleep cycles	Mean sleep cycle length*
KB	56.3	91.7
FC	59.5	116.2
MC	65.3	94.0
JG	78.1	106.3
GH	75.8	114.9
AH	63.3	112.1
WH	47.2	82.8
RMCD	59.7	100.1
GJ	77.3	119.5
JR	59.5	97.4
RR	84.7	120.6
MS	41.4	94.9
MT	40.9	114.8
FW	58.0	90.4
AW	66.4	105.5
MW	75.2	122.1

NOTE: \*Raw data in Table 10.1.

Correlation coefficient (r):

Between mean sleep cycle length and the mean amount of  
REM sleep accumulated in the first three sleep cycles.

$r = 0.575$ ,  $p < 0.03$ ,  $df = 14$  (2-tailed).

TABLE 10.6. SLEEP CYCLES AND BODY WEIGHT.

Partial correlations between mean sleep cycle length, mean total sleep time (TST) and mean percentage deviation from ideal body weight (% IBW).

Notation:  $r_{12.3}$  = partial correlation between variables 1 and 2 with the effect of variable 3 eliminated and  $r$  = the usual Pearson's product-moment correlation between two variables. (Raw data in Table 10.3).

(a) Sleep cycle length(1) v. % IBW(2)

$$r = 0.563$$

$$r_{12.3} = 0.370 \text{ (effect of TST eliminated)}$$

∴ 57% of the association between 1 and 2 due to their associations with total sleep time.

(b) Sleep cycle length(1) v. total sleep time(2)

$$r = 0.572$$

$$r_{12.3} = 0.387 \text{ (effect of \% IBW eliminated)}$$

∴ 54% of the association between (1) and (2) due to their associations with percentage deviation from ideal BW.

(c) Total sleep time(1) v. percentage deviation from IBW (2)

$$r = 0.536$$

$$r_{12.3} = 0.316 \text{ (effect of sleep cycle length eliminated)}$$

∴ 65% of the association between (1) and (2) due to their associations with sleep cycle length.

CHAPTER 11

GENERAL DISCUSSION AND A SUMMARY OF CONCLUSIONS

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## CHAPTER 11

### GENERAL DISCUSSION

The experiments and subsequent treatments of the data described in Chapters 3 to 10<sup>are</sup> documented in their chronological order. The results of each section are discussed in the light of the results of the preceding experiments and not in relation to studies which followed them. The present section is a general overview of all the results and the questions they provoked, discussed in the light of what I know now and how some of my results perhaps provide an explanation of the apparently contradictory reports in the literature, about the effects of bedtime eating on sleep.

(a) Is bedtime nutrition comparable to hypnotic drugs in promoting sound sleep?

The simple answer to this question is obviously no, when the results of Parts 3 and 4 of Chapter 3 are compared. There was a striking difference between the efficacy of nitrazepam in prolonging sleep and reducing the interruption of sleep by wakefulness in contrast with the total lack of effect of Horlicks at bedtime on subsequent sleep. In that experiment no restrictions were imposed on the subjects' eating and drinking in the/

the later evening. In retrospect, had the subjects in that study been a group of people who normally ate a snack at bedtime and had they been instructed not to eat or drink anything after about 1900h then I think the results would have been entirely different and the bedtime food drink might well have appeared as effective as the drug over prolonged use.

(b) Is drugged sleep as good as natural sleep?

The question cannot be adequately answered until research is done to develop quantitative measures of the restorative properties of sleep. Changes in the electrophysiologically-recorded pattern of sleep tells us that a drug has prolonged the duration of sleep, but nothing about any changes in the underlying processes, so we cannot tell if a minute of drugged sleep is 'worth' more or less than a minute of natural sleep, in terms of restorative power. Slow wave sleep and REM sleep are often reduced or disrupted by drugs and these are the stages of sleep that are thought to be particularly associated with the restorative functions of sleep (Oswald, 1969, 1970, 1973, 1976; Hartmann, 1973; Stern and Morgane, 1974). We do not know if the reduction, by the criteria of electrophysiological recordings, in the amount of a sleep stage, is associated with a comparable impairment in the biological functions/

functions of the sleep stage. The only indicator we have at the moment in humans is the sleep-dependent nocturnal secretion of growth hormone, which of course may not be a comprehensive measure of the biological functions of slow wave sleep. It has been reported by me in Chapter 3, Part 4, and by others before me, that benzodiazepine drugs reduce the number of min recorded in slow wave sleep (refs in Chapter 3, Part 4). However, when the associated growth hormone secretion was investigated no parallel diminution was found, as reported in Chapter 4 and by others (Stokes et al., 1972; Rubin et al., 1973b; Bixler et al., 1976). This can be interpreted in a number of ways. It could indicate that the association between nocturnal growth hormone secretion and slow wave sleep (SWS) is not a proportional one but rather that SWS acts as a trigger to promote growth hormone secretion and thus only a few min of SWS provide the necessary stimulus. The latter interpretation is supported by the fact that even in the undrugged state those whose sleep usually includes a lot of SWS are not necessarily those who secrete relatively more growth hormone and visa versa (Table 4.6 and e.g. Schnure et al., 1971). An alternative explanation could be that the drug-induced reduction in min of SWS initially leads to a reduction in the biological processes associated with this type of/  
of/



of sleep but that over time there is an adaptive change so that the min spent in SWS become, so to speak, more biologically efficient. An indication that this may be true was reported by Stokes et al. (1972) who found that nocturnal growth hormone secretion was slightly decreased on the first two nights of diazepam administration. Since our study (Chapter 4) and the others did not measure growth hormone secretion on the first few nights on the drug we may have missed an initial depression of nocturnal growth hormone secretion. The Stokes et al. (1972) study only involved two subjects so no statistical evaluation was possible thus the question really remains unanswered for the present.

As I said earlier, growth hormone (GH) secretion may not be a direct measure of the biological role of SWS. GH is an anabolic hormone that promotes protein synthesis (Korner, 1965) but obese patients secrete only very small quantities of GH in response to SWS (Kalucy et al., 1976) and as one must assume that restoration and repair still occur in these patients this suggests that the nocturnal secretion of GH is a facilitatory and not obligatory accompaniment to the restorative processes associated with sleep.

A/

A more direct index of the restorative power of sleep would be a measure of net protein synthesis, which of course must occur if you believe that sleep is a time for tissue synthesis and repair. The few studies investigating nitrogen metabolism during drugged and drug-free sleep in humans have been done in patients undergoing 'therapeutic sleep'. The induction of sleep for therapeutic purposes involves keeping patients asleep for the majority of the 24h of each day for a period of weeks. Sleep is induced either by low doses of hypnotics, tranquillizers or by a conditioned reflex technique. The conditioned reflex (CR) induction method does not involve drugs and so the comparison between nitrogen retention during say, barbiturate induced therapeutic sleep and CR sleep, could give an indication of a difference between drugged and natural sleep. According to Kühn (1963) barbiturate-induced sleep led to positive nitrogen balance over a two-week period whereas CR sleep was associated with a negative nitrogen balance over a similar period. I should point out that the experimental subjects were hospital patients and although the author did not specify their ailments the usual reasons for sleep therapy treatment are e.g. for nervous and/

and mental illness, gastrointestinal problems, or post-operative cases, conditions which might be expected to lead to negative nitrogen balance. What we are not told in this study is how much sleep was achieved under either treatment and whether the patients in each group were matched for ailments and so it is difficult to interpret the results.

Voronka and Rubinskaya (1974) have studied the effects of low and high doses of barbiturate on the protein and RNA content of neurones and glia of rat supra-optic nucleus. They found that a low dose of barbiturate was associated with enhanced protein and RNA content compared with undrugged control rats, whereas a high dose of barbiturate depressed the RNA and protein content. These studies may suggest that low doses of barbiturates do not impair synthetic processes but a lot more work will have to be done before any definite conclusions can be drawn.

I have only considered the restorative value of drugged sleep in comparison with natural sleep, but hypnotic drugs are taken by people who feel that their natural sleep is inadequate and so the distortions of sleep caused by drug administration must be balanced against the presumably detrimental effects of broken and/



and/or shorter sleep. Perhaps a more pertinent point is that the belief that sleep is inadequate can cause anxiety which can lead to elevated corticosteroids. Subjects who described themselves as poor sleepers were found to have higher corticosteroid levels during the night than a group of subjects who rated themselves as good sleepers (Monroe, 1967). Corticosteroids are generally catabolic hormones and enhance amino acid degradation and reduce protein synthesis (Friedman and Strang, 1966; Ardeleanu and Sterescu, 1973) and so elevated corticosteroids will oppose synthetic processes, with the net effect of impaired recuperation during sleep. So if drugs can attenuate a patient's anxiety about the quality of his/her sleep then the detrimental effects of anxiety will also be reduced. This supposition has not been extensively investigated but a study of two tranquillizers did find that plasma corticosteroids were reduced during drug administration (Ogunremi et al., 1973). However, the crucial question has not been answered, namely, does an increase in sleep duration and reduction in anxiety achieved by drugs offset deleterious effects (if any) of the distortion of the amount and distribution of sleep stages by hypnotic drugs?

(c) Previous studies into bedtime nutrition and sleep - can the sometimes contradictory results be explained?

In Chapter 2, I referred to a number of different studies which have investigated the effects of bedtime nutrition on subsequent sleep. Taken at face value, the results of these studies are contradictory, but on closer inspection of the results or the experimental methods, some of them may, perhaps, be explained in the light of the results of my studies.

For example, Giddings (1934) reported that after a drink of warm milk at bedtime 41.7% of the children in his study had fewer body movements during the night when compared with the nights when they had had nothing to eat or drink before bed. In 8.3% of the children motility was increased after the milk drink and in 50% there was no difference. He interpreted this as meaning that drinking 6 oz of milk at bedtime produces quiet sleep in normal children. What he did not comment on was that the children who slept more peacefully after milk did so consistently over the five nights recorded and similarly for those whose sleep was unaffected or made more restless after milk. This would appear to be an example of individual differences in the response to bedtime nutrition which may be due to differences in the usual dietary habits of the children.

Laird/

Laird and Drexel (1934) investigated the effects on nocturnal motility of a 'hard to digest', but unspecified, snack compared with an 'easy to digest' snack of milk and cornflakes at bedtime. They found that sleep was less restless after the milk and cereal food snack. I found that when a bedtime food drink based on soya (flavoured drink) was taken the subsequent sleep was more broken by wakefulness than sleep after the malted milk and cereal beverage, Horlicks, at bedtime (Chapter 5). If the soya-based product was less easily digested than the milk and cereal drink then my results would seem to confirm those of Laird and Drexel.

Kleitman et al. (1937) studied nocturnal motility in subjects after a number of different bedtime nutritional intakes and found that sleep was less restless after the milk and cereal bedtime food drink, Ovaltine, than after hot milk alone. I found that sleep was less broken after Horlicks than after milk alone and so my results would appear to be comparable. They also compared motility after hot milk with that after nothing to eat or drink and found no significant difference and I too, found no significant differences between milk and a placebo capsule on various measures of sleep. Included in their experiment was a comparison between/



between Ovaltine in hot milk and nothing to eat or drink. They found that, on average, the sleep of 20 subjects was less restless, but one subject showed no change and, in seven, sleep was more restless after Ovaltine. So in about a third of their subjects sleep was more restless after taking Ovaltine at bedtime. A comparable proportion was found in my study (Chapter 6) into the effects of dietary habits on sleep. The benefit to sleep from a bedtime food drink was presented as the mean difference in min of, say, total time spent asleep over the five nights recorded on the food drink minus the mean min recorded over the five nights recorded when capsules had been taken at bedtime (for measures of wakefulness the mean on a food drink was subtracted from the mean on capsules). A negative difference represents poorer sleep and inspection of Table 6.5 shows that 5 out of 16 subjects slept, on average, for a shorter length of time when Horlicks had been taken at bedtime, compared with sleep after capsules. Table 6.6 shows that 5 out of 16 subjects had more wakefulness between the first onset of sleep and the end of recording when they had taken Horlicks compared with when they had taken capsules at bedtime and similarly Table 6.7 shows that 6 out of 16 subjects had more wakefulness interrupting the first 6h of sleep after Horlicks than after capsules. These three examples from my data illustrate that about a third/

third of my subjects slept worse after taking Horlicks at bedtime in comparison with nothing to eat or drink - this proportion of about a third is the same as reported by Kleitman et al. (1937) in a comparison of Ovaltine with nothing to eat at bedtime.

Hamilton et al. (1966) investigated the influence of a bedtime snack of cereal and milk on nocturnal motility, over a number of nights, in comparison with sleep after nothing to eat at bedtime. The experiment was carried out in two groups: a group of nine middle-aged convalescent tuberculosis patients and a group of 27 young monastery students. The authors found no differences between the two conditions of bedtime intake in either group of subjects. The authors also reported that not one subject displayed a significant difference in nocturnal motility between the two conditions of bedtime intake. These results at first appear to contradict my and those of others findings. I wonder if the rather unusual subjects selected to take part in the Hamilton et al. (1966) study are the reason for the discrepancy. Young men living in a monastery were probably adapted to a more spartan way of life, which I am sure would not have included the luxury of a snack at bedtime, and in any case young men usually sleep so well that there is little room for improvement. The other/

other group in Hamilton's study were hospital patients. The authors gave no information about any medication taken by these patients and I suspect they may well have been taking hypnotics and a bedtime snack has been shown to be no match for an hypnotic drug in its ability to promote sound sleep (Chapter 3).

Finally, Březinová and Oswald (1973) reported that in a comparison between Horlicks and a placebo capsule at bedtime, Horlicks was associated with sleep of longer total duration and with less interruption by waking. In Chapter 7, I reported a post-hoc division of my 16 subjects into two groups of eight. The criteria for allocation of a subject to one group or the other depended on the rank order of his/her N% score. It was predicted that those with higher N% scores, the bedtime 'Eaters' group (that is those who usually eat relatively more food at bedtime), would sleep better after Horlicks than after a placebo capsule at bedtime. The bedtime Eaters group were found to sleep better after Horlicks than after capsules, which led me to speculate that the subjects in the Březinová and Oswald study were predominately drawn from those who habitually have a snack in the later evening and that those authors were in fact measuring the detrimental effects of the lack of bedtime nourishment after/



after the capsule and not an improvement in sleep attributable to Horlicks.

To summarize this overview of some of the literature on the effects of bedtime nourishment on sleep, it appears that one can, to a certain extent, manipulate the outcome of a study of the effects of bedtime eating on sleep by the selection of subjects according to their later evening dietary habits and by imposing a restriction on their food and drink intake in the later evening. The results of any study comparing sleep after bedtime nourishment with nothing to eat, if achieved with the latter restriction, should be interpreted with caution because the results may be more representative of deprivation of nourishment at bedtime than any sleep-promoting qualities of the food at bedtime. A disturbance of a person's habitual pattern of food intake is likely to disrupt sleep.

(d) Examples of the disruption of habitual eating patterns affecting sleep.

Chronic undernutrition is an extreme example of disrupted eating habits. In a retrospective study of survivors from prisoner of war camps and civilians who had been on meagre rations of food, it was reported that about 50% of the victims complained of insomnia (Russel Davis, 1951).

Voluntary/

Voluntary restriction of overall calorie intake has been shown to disturb sleep, for example, during therapeutic loss of weight on a very low calorie diet, obese patients reported that they slept less (Crisp et al., 1973) and when anorexia nervosa patients were well below their normal weight their sleep was of shorter total duration and more fragmented by waking (Crisp et al., 1971; Lacey et al., 1975).

Rats kept short of food are more restless and sleep less than normal (Jacobs and McGinty, 1971) and motility in babies is proportional to the time that has elapsed since they were last fed (Irwin, 1932). Wada (1922) simultaneously recorded hunger contractions of the stomach and body movements in one sleeping subject and found that powerful stomach contractions were often synchronous with a period of restlessness.

It is not clear if it is the loss of body weight or the hunger associated with an inadequate intake of food that is responsible for the loss of sleep associated with under-nutrition. The ten anorexia nervosa patients in the Lacey et al. (1975) study were fed approximately the same number of calories throughout the period of weight gain and yet over that period their sleep increased in duration and became less broken by wakefulness, suggesting that it was the restoration/

restoration of body weight that was responsible. Crisp and Stonehill (1973) reported an investigation of 375 psychiatric out-patients. The patients' recent sleep and their sleep before their illness was assessed by one interviewer and another assessed their present and prior body weight. All the patients were independently rated for mood and other psychiatric variables by a psychiatrist. It was found that loss of weight was associated with poorer sleep and gain in weight with increased sleep and these relationships were independent of age, mood or psychiatric status. The latter two studies suggest that it is change in body weight that is primarily responsible for the changes in sleep.

I found a correlation between the degree by which a person was over or under-weight and their mean total sleep time (Chapter 10), in subjects whose body weights were stable. The degree of over or under-weight for height is correlated with the amount of adipose tissue (Hume and Weyers, 1971; Durnin and Womersley, 1974) and so it may be that there is an association between body fuel stores and the rhythm of sleep and wakefulness. I found that both the mean total sleep time and the percentage deviation from ideal body weight were significantly correlated/



correlated with the mean NREM-REM sleep cycle length (Chapter 10). It is possible that changes in body weight may lead to alterations in the sleep cycle length which, in turn, are responsible for changes in the total duration of sleep.

The foregoing discussion considered the disruption of sleep by an overall reduction in the habitual intake of calories and the associated loss of weight. Transmeridian travel by air and rotating shift work both disturb the usual pattern of eating. Rapid travel to another continent imposes a new environment, with meal times which are out of phase with the traveller's internal rhythms of feeding and this can mean that a newly arrived traveller eats dinner when, according to his endogenous rhythm, he would be asleep. In my study of the influence of customary dietary habit on the effects of bedtime food on sleep (Chapter 6) I found that when someone who normally did not eat at bedtime was given food at that time, even something as innocuous as a cup of hot milk, then their sleep was impaired. It is thus easy to see how eating a substantial meal at an unaccustomed time could disturb subsequent sleep. If the traveller remains in the new environment for a sufficient length of time, his internal rhythms will/

will gradually synchronize with those of his surroundings. The time it takes will naturally depend on by how many hours the endogenous and exogenous rhythms are out of step and on the age of the traveller. But, a worker involved in a schedule of rotating shifts, where for example, one week he is on night shift, the next week on day shift followed by a week on the evening shift, will never fully adjust his internal rhythms to any particular shift. It is not surprising that indigestion is a frequent complaint of workers on this type of shift work (Conroy and Mills, 1970).

The experimental design of my study (Chapter 5) to investigate the effects of bedtime eating on sleep allowed subjects 15 nights on a treatment before coming to the sleep laboratory, and yet the influence of their usual bedtime dietary habits was still present when the recordings were made, which suggests that the detrimental effects on sleep following a change in eating pattern persists, and that it may take much longer than two weeks fully to adjust, at least in older people, to a new regime.

(e) What is the function of REM sleep?

It has been generally supposed that because NREM and REM sleep are qualitatively different both physiologically and in terms of neural mechanisms, then the underlying functions must be different. Until recently, speculation about the roles of REM sleep appeared to be limited to the brain and somatic correlates for the amount of REM sleep were not even contemplated. It was NREM (orthodox sleep) that had been assigned any supposed functions related to bodily growth and repair. I see no reason why both categories of sleep should not have many functions, which encompass the whole body.

The aspects of REM sleep that have particularly pointed to an association with brain function include the high proportion of REM sleep in babies (and young animals) when the brain is still growing (Roffwarg et al., 1966), the decline in amount when the brain shrivels in senility (Feinberg et al., 1967), the disproportionate and prolonged increase in amount of REM sleep following poisoning by CNS-affecting drugs (Oswald, 1969; Haider and Oswald, 1970) and the lower-than-normal quotas found in the mentally retarded (Petre-Quadens and Jouvet, 1966; Feinberg et al., 1969; Castaldo and Krynicki, 1973, 1974) and in deaf children (Stojanović and Dürriq), 1975 whose information/



information processing is presumed to be impaired. Oswald (1969, 1970, 1976) has seen some of these as evidence for REM sleep being associated with the restoration and repair of brain tissues and more particularly with brain protein synthesis. Others have specified that they believe that REM sleep is not only associated with, but it a stimulus to brain protein synthesis e.g. (Drucker-Colin et al., 1975a). There are, however, fundamental reasons, outlined in Chapter 1 why the latter is unlikely to be the case.

Other biological theories have been suggested and include the proposal that REM sleep serves to clear the brain of some product accumulated during NREM sleep (Hartmann, 1973) or that it provides an endogenous source of stimulation to the developing brain of the neonate (Roffwarg et al., 1966), that it reorganizes neuronal firing patterns, disorganized by NREM sleep (McGinty et al., 1974), that it may play a role in maintaining the functioning of the catecholamine neurones in the central nervous system (Stern and Morgane, 1974).

It has also been proposed that REM sleep serves a behavioural role periodically to alert mammals to be ready for flight or fight and the evidence for this is that predators have less REM sleep than those who are potential prey (Snyder, 1966). This latter theory/

theory appears rather naive; surely to awaken at intervals would be preferable for the preyed-on animals?

Probably because of the association between REM sleep and dreaming, it has been thought by the general public, and some sleep researchers as well, that the function of REM sleep is for dreaming and that this is necessary for mental health. Early studies of REM sleep deprivation reported dramatic changes in psychological state and suggested that REM sleep was needed to maintain mental health (e.g. Dement, 1965; Dement et al., 1966). However, recent studies have failed to replicate these findings or even find minor psychological changes in subjective mood (reviewed by Dement, 1970) so that now, even Dement, who perpetrated the idea, is critical of his original notion that adequate amounts of REM sleep were necessary for mental health. Other psychological theories of the function of REM sleep suggest that it is related to the regulation of motivated behaviour, evidenced by the pronounced aggressive and sexual behaviour and increased food consumption subsequent to REM sleep deprivation in cats (Dement et al., 1967). But this distorted behaviour may be due to the non-specific effects of stress associated with REM sleep deprivation (Mendleson et al., 1973). Siegel (1975) sought to determine if there was a relationship between spontaneous/

spontaneous variations in the amount of REM sleep and motivated behaviour in cats, measured by the quantity of food they ate. He found that the min of REM sleep in a 12h period was an accurate predicator of the amount of food eaten in the subsequent 12h. He found the greater the amount of REM sleep, the smaller the amount of food eaten in the following 12h, which suggests to me that REM sleep is related to energy regulation. There was apparently no significant correlation between the amount of REM sleep and the food intake in the previous 12h. However, studies of caloric regulation, in human subjects with constant body weights, have shown that the balance between calorie expenditure and intake is not achieved on a day to day basis, but over a number of days (Edholm et al., 1970; Spiegel, 1973). Thus the quota of REM sleep on any one night could be reflecting the food intake of several days earlier and not just the previous day. During acute starvation in normal volunteers, the min spent in REM sleep (and the percentage of REM sleep) declined over the four days without food (MacFadyen et al., 1973). This could be interpreted as a reduction in REM sleep associated with the need to eat more food to maintain body weight. Similarly, in starving rats the amount of REM sleep fell over a number of days and disappeared in the majority/



majority (5 out of 7) of rats after an average of 8 days without food (Jacobs and McGinty, 1971). However, Lacey et al. (1975) found that the amount of REM sleep was about 29% (100.9 min compared with 141.8 min) lower when their anorexia nervosa patients were about 30% below target weight, than when they had regained their target weight. The important point is that their calorie intake was approximately the same when the two sets of recordings were made, which suggests that it is changes in body weight (and perhaps fuel stores) that are associated with changes in REM sleep. It would be interesting to see how much REM sleep anorexia nervosa patients achieve when restricting their energy intake.

And finally, I have found (Chapter 8) that the amount of REM sleep is correlated with the stable body weights of 16 middle-aged subjects.

It is difficult to form a cohesive hypothesis, from the reports above, relating stable body weight, changing body weight, food intake, energy expenditure and the quota of REM sleep. A possible hypothesis might be when body weight is stable, energy expenditure and food intake must be equal over time, but on a daily basis they may not and so body weight (or fat stores) may vary from day to day but be stable over time. Small increases in body weight are associated with increases/

increases in an individual's quota of REM sleep, which in turn is associated with a signal to consume less food during the following day to compensate for the over-eating of a previous day(s) and so restore the body to its 'usual' weight. The hypothesis can explain the reduction in REM sleep during starvation, because the lack of food means that energy expenditure far exceeds intake and so the body weight falls, consequently the amount of REM sleep falls, and this is associated with a signal to eat more as body reserves have been depleted.

There are several problems for this theory, e.g. the young have, on average, more REM sleep than older people and yet the former also tend to be lighter. However, the daily energy expenditure of a young person is usually higher than that of an older person of comparable body weight. It may be that it is the daily energy expenditure that is the important factor in adults and that within an age group this correlates highly with body weight. Other factors must, of course, be related to an individual's quota of REM sleep and the relative contributions of these may vary according to age.

The question arises as to what determines the 'usual' body weight over a period of time. The hypothesis outlined above may indicate a mechanism whereby/

whereby body weight is regulated through changes in appetite, even although especially in man, this can be overridden by external factors. If this hypothetical mechanism does operate, it suggests that, associated with REM sleep, there is a homeostatic process operating which is sensitive to, and perhaps compensates for, the energy expenditure, and so for the cellular work of the preceding waking period. Muscle metabolism accounts for a large percentage of whole-body oxygen consumption. REM sleep is characteristically associated with loss of muscle tone and so might have a compensatory role for the extent of daytime activity. The amount of compensation (as min of REM sleep) would depend on energy expenditure and so on body weight, and could signal how much energy intake might be required the following day.

(f) Is sleep cycle duration associated with the regulation of body weight?

I found that the mean sleep cycle length was correlated with the degree by which a person was over or under-weight (Chapter 10). This was found in subjects with stable body weights and so I cannot say whether the sleep cycle duration is dependent on the percentage deviation from ideal body weight or if the sleep/



sleep cycle length is an inherent characteristic of a person's sleep. The latter would suggest that a person may be predestined to be over or under-weight. It would be very interesting to see if loss or gain of body weight would alter the mean sleep cycle length.

Březinová (1974b) reported that longer sleep cycles contained significantly more slow wave sleep and REM sleep than shorter cycles matched for serial order and I found that subjects who had, on average, sleep cycles of longer duration also tended to accumulate more REM sleep over the first three sleep cycles (Table 10.5, Chapter 10). I can envisage a mechanism where weight gain in an individual leads to lengthening of sleep cycle duration and where there is an associated increase in REM sleep accumulated. The increase in REM sleep then would act as a signal to reduce food intake. However, this signal must be very feeble in humans!

I found that mean total sleep time was significantly correlated with the degree by which a person was over or under-weight (Chapter 10) and Crisp et al. (1973) reported that their obese patients slept less as they lost weight and Crisp et al. (1971) and Lacey et al. (1975) found that as anorexia nervosa patients slept more as they approached their target weight. I also found/

found that mean sleep cycle duration was significantly correlated with both mean total sleep time and percentage deviation from ideal body weight and I would predict that as obese patients lose weight their sleep cycles would become shorter and when underweight patients gain weight, their sleep cycles, would, on average, increase in length.

If the above is true it still cannot, as yet, be said whether a change in sleep cycle length associated with an alteration in the degree of under or over-weight has any homeostatic role or whether it is just an associated phenomena due to some alteration in metabolism.

SUMMARY OF GENERAL CONCLUSIONS FROM MY EXPERIMENTS

1. Eating at bedtime is not a universal panacea for promoting more restful sleep. It only aids the sleep of those who habitually eat at bedtime.
2. In those who normally do eat something prior to retiring to bed, a combination of cereal and milk is recommended, in preference to other types of food, as more likely to promote restful sleep.
3. I could find no evidence of any changes in sleep attributable to a placebo, in my group of ten healthy middle-aged volunteers.
4. Nitrazepam, 5mg nightly, is a lastingly effective hypnotic, but its withdrawal leads to disrupted sleep for many nights. Chronic administration does not impair nocturnal growth hormone secretion.
5. Nocturnal plasma triglycerides are elevated when a milk and cereal food drink, Horlicks, is taken every night by older people over a number of weeks and because of this it should probably be avoided by those prone to atherosclerotic disease.
6. REM sleep may have a function for restoration and repair of the body in addition to any it may have for the brain. It may have a role in energy balance.
7. Sleep cycle duration may be related to body weight regulation.



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## Subjective ratings of sleep quality and anxiety after placebo, drug and a food drink

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### Summary

Ten subjects (mean age 57 years) took part in a cross-over study between a food drink and nitrazepam 5 mg. They rated their anxiety and sleep quality. On half the sleep laboratory nights during baseline periods subjects were given an inert pill which they were told would improve sleep. A comparison was made between the six pill and six non-pill nights for each subject. Subjective ratings revealed no significant difference attributable to the inert pill. Sleep quality was rated to have been improved during both late drug and early food drink administration. On early drug withdrawal sleep quality was rated worse than baseline.

### Introduction

There have been very few studies of the effect of placebo on sleep, and yet this is an important consideration when a treatment is administered whose nature cannot be disguised, and with which subjects may associate an effect. In a study comparing placebo, flurazepam and no treatment, Kales *et al.* (1971) demonstrated no effect of placebo on sleep induction, maintenance, stages or on subjective assessment of sleep quality. Davis and Hartmann (1973) recorded subjects electrophysiologically and found no significant difference in total sleep time and sleep onset latency between the means of three placebo and three treatment nights. In a later experiment, comparing the EEG recordings of subjects on placebo for 28 days with a preceding baseline period, Hartmann and Cravens (1973) believed they had found a rather tenuous connection between placebo administration and an increased amount of REM sleep which continued into early withdrawal from placebo. The present study differs from those mentioned above in that our subjects were told that the inert pill would have a beneficial effect on their sleep and hence more specifically investigated the power of suggestion.

### Methods

Ten healthy subjects aged 41-62 years (mean 57 years) took part in a cross-over study between a food drink and nitrazepam 5 mg.

Subjects attended the sleep laboratory in pairs differing from each other for the experimental condition. Each subject slept in quiet and comfortable conditions on a total of 58 nights spread over 38 weeks according to the experimental design in Table 1.

TABLE 1. The experimental design used

Week No.	Treatment
1 and 2	2 Adaptation nights 6 Baseline nights
5 and 6	1 Adaptation night 6 Early treatment nights
7, 8, 9 and 10	Treatment continued at home
11 and 12	1 Adaptation night 6 Late treatment nights
13 and 14	Treatment continued at home
15 and 16	1 Adaptation night 6 Withdrawal nights

Six weeks later, subjects repeated the above schedule on the alternative treatment. Treatments were administered about 30 min before lights out (approximately 10.30 p.m. to 7.30 a.m.).

Subjects rated their own sleep quality in the morning and in the evening rated their daytime anxiety using visual analogue scales (0-100 mm) where sleep quality ranges from 'worst' to 'best' and anxiety from 'terrible agitation' to 'imperturbable tranquillity'.

On half the baseline nights and in balanced order each subject was given a pink placebo pill. They were told that these would 'help make your sleep more restful without causing any hangover'. The food



drink was made with 32 g of Horlicks powder mixed with 250 ml of hot milk. The drug and the food drink were each taken for 10 weeks by every subject.

### Results

Ignoring the subjective ratings collected on the adaptation nights, each of the ten subjects had a total of twelve baseline nights (six pill and six non-pill) and six laboratory nights for each of the other experimental conditions.

Friedman's analysis of variance (Siegel, 1956) of the subjective ratings from both baseline periods demonstrated that when the inert pill had been taken the night before neither sleep quality improved ( $\chi^2 = 3.45$ , d.f. = 3, n.s.) (Table 2) nor anxiety altered ( $\chi^2 = 1.32$ , d.f. = 3, n.s.) (Table 4).

TABLE 2

Subjective sleep quality	mean $\pm$ s.e. (in mm)
Mean baseline: pill	45.6 $\pm$ 2.4
non-pill	49.2 $\pm$ 3.3 n.s.
	47.4 $\pm$ 2.6

TABLE 3

Subjective sleep quality	mean $\pm$ s.e. (in mm)
Mean baseline	47.4 $\pm$ 2.6
Early drug	50.1 $\pm$ 2.9
Late drug	53.0 $\pm$ 3.0†
Drug early withdrawal	39.9 $\pm$ 3.0*
Early food drink	50.7 $\pm$ 2.7†
Late food drink	49.8 $\pm$ 2.3
Food drink early withdrawal	50.7 $\pm$ 2.6

\* significantly lower than baseline at  $P < 0.05$  level (1-tailed test)

† significantly greater than baseline at  $P < 0.025$  level (1-tailed test)

Sleep quality was rated to have been improved during both the late drug ( $t = 2.28$ ,  $P < 0.025$ , 1-tailed) and early food drink ( $t = 2.63$ ,  $P < 0.025$ , 1-tailed) administration, when correlated  $t$ -tests were used to compare them with baseline (Table 2).

A difference between subjective ratings of sleep quality was seen when comparing the baseline mean

TABLE 4. Subjective anxiety ratings for the day before and the day following a night spent at the sleep laboratory

	Mean $\pm$ s.e. (in mm)
Before	
Mean baseline: pill	51.8 $\pm$ 1.8
non-pill	52.9 $\pm$ 2.1 n.s.
After	
Mean baseline: pill	52.7 $\pm$ 1.9
non-pill	51.2 $\pm$ 1.7 n.s.

with early withdrawal (laboratory nights 1, 2 and 3 from the drug, i.e. sleep being rated worse after drug withdrawal ( $t = 1.88$ ,  $P < 0.05$ , 1-tailed).

No significant differences were found between the baseline anxiety rating and any subsequent treatment.

### Discussion

Any experiment which sets out to investigate the value of a treatment whose identity cannot be concealed is faced with the problem of how big a partial suggestion may play in the results. In this experiment subjects were specifically told that their sleep would be improved and yet this was not reflected in the subjective ratings. The results of the EEG sleep recordings made on the nights when subjects attended the laboratory appear also unaffected by placebo but will be reported at a later date.

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## $\alpha$ -ADRENERGIC RECEPTOR BLOCKADE INCREASES HUMAN REM SLEEP

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1 An  $\alpha$ -adrenergic receptor blocking agent, thymoxamine (150 mg i.v.) in the early night sleep of young adults increased REM sleep duration and also brief awakenings in the early night, while slow wave sleep, stage 3 + 4, was diminished. In the later night, however, stage 3 + 4 sleep was increased. Control experiments demonstrated that thymoxamine (i.v.) was without effect on blood pressure.

2 REM sleep duration may be inversely proportional to noradrenaline available at central  $\alpha$ -adrenoceptors, but the control mechanisms for REM sleep appear interdependent with those for NREM sleep.

### Introduction

The possible role of brain amines in sleep has attracted much interest. After imipramine or related compounds such as desipramine (Dunleavy, Brezinová, Oswald, MacLean & Tinker, 1972), or after amphetamine derivatives (Oswald, 1970), rapid eye movement (REM) (paradoxical) sleep is reduced in duration, and intra-sleep restlessness (frequency of transitions into drowsiness or wakefulness) is increased. It is commonly hypothesized that both these groups of drugs increase noradrenaline at post-synaptic receptors, in the one case through reduced re-uptake and in the other through greater release. Consequently, in an earlier experiment, propranolol was investigated, a drug believed to block the action of noradrenaline on  $\beta$ -adrenergic receptors and known readily to enter the brain. An oral dose of 120 mg at bedtime had no effect itself on sleep and did not modify the reduction of REM sleep by imipramine (75 mg) or by dexamphetamine sulphate (10 mg) (Dunleavy, MacLean and Oswald, 1971). We have now investigated an  $\alpha$ -adrenergic receptor blocking agent, thymoxamine, administered intravenously.

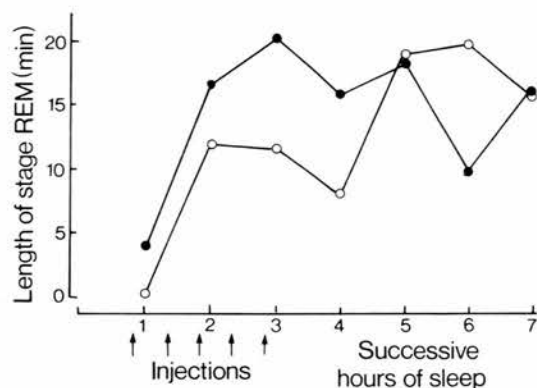
$\beta$ -adrenergic receptor blocking agents are used clinically to lower blood pressure. We had no reason to believe thymoxamine would do so in recumbent persons (and no reason to think that change of blood pressure would affect REM sleep) but as a control have conducted a secondary experiment to determine whether thymoxamine could alter blood pressure.

### Methods

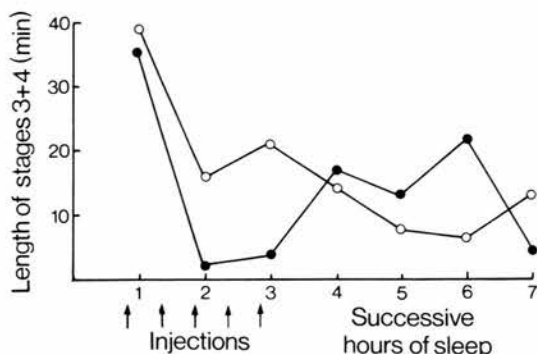
Ten healthy young adults slept three nights each in the laboratory at approximately weekly intervals, with recording of all-night electroencephalogram (EEG), electro-oculogram (EOG) and submental electromyogram (EMG) at 15 mm/second. A forearm vein catheter was connected with an extension that passed through the bedroom wall. The catheter 6 ml dead space was filled with saline, containing heparin (20,000 i.u./litre). The first night was for adaptation. Saline or thymoxamine was injected on the other two nights, the order being balanced. Five injections were given, at 50 min after first stage 2 sleep onset, and then at 30 min intervals. Injections were of 10 ml, each given during approximately 2 min, either saline with thymoxamine (30 mg) or saline alone.

It was assumed that high blood levels of thymoxamine would exist in the second, third and fourth hours of sleep and, because of pilot experimental results, a specific prediction was made that in these hours enhancement of REM sleep duration would be caused. When recordings were complete the all-night electrophysiological records were coded and scored blind for stages of sleep (Rechtschaffen & Kales, 1968). Raw scores were processed by computer to give amounts and hour by hour distribution of all sleep stages, and episodes of wakefulness.

In order to investigate the blood pressure effect of i.v. thymoxamine (30 mg) in recumbent persons, six healthy young male adults lay for 3 h



**Figure 1** Thymoxamine (●) (30 mg  $\times$  5, i.v.) during the early night increases REM sleep duration when compared with saline (○). The results are the mean for ten subjects.



**Figure 2** Thymoxamine (●) (30 mg  $\times$  5, i.v.) decreases slow wave sleep stage 3+4, with later apparent compensatory increase when compared with saline (○). The results are the mean for ten subjects.

in bed and their blood pressures were recorded every 5 min by clinical sphygmomanometry, to the nearest 5 mm of mercury. After 20 min each was given an i.v. injection of saline (10 ml) into the other forearm and 15 min later a test dose of thymoxamine (15 mg) in saline (10 ml). Then after 25 min the first of four injections of 10 ml at 20 min intervals was given. Two were of thymoxamine (30 mg) in saline (10 ml) and two of saline only. The sequence was ABAB, with three men receiving saline first and three thymoxamine first. The order of injections was not known to the experimenter recording the blood pressure, nor to the subjects.

## Results

Three features only of sleep were altered by the thymoxamine injections compared with saline.

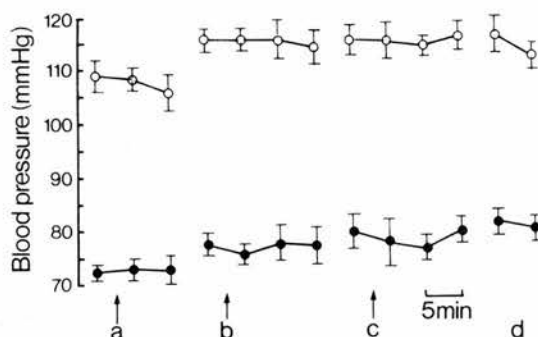
**REM sleep (Figure 1):** in hours 2-4 mean hourly REM sleep on saline nights was  $10.5 \pm 3.0$  min and on thymoxamine nights  $17.6 \pm 7.6$  min ( $t$ -test for paired observations,  $t = 2.92$ , d.f. = 9,  $P < 0.01$ , 1-tailed). In hours 5-7 REM sleep with saline was  $18.5 \pm 4.1$  min but  $15.3 \pm 4.7$  min with thymoxamine (NS). **Stage 3+4 sleep (Figure 2):** in hours 2-4 mean hourly stage 3+4 on saline nights was  $17.3 \pm 6.7$  min and on thymoxamine nights  $7.6 \pm 6.4$  min ( $t = 3.85$ , d.f. = 9,  $P < 0.01$ , 2-tailed). In hours 5-7 stage 3+4 with saline was  $9.0 \pm 4.1$  min but  $12.8 \pm 7.6$  min with thymoxamine ( $t = 2.45$ , d.f. = 9,  $P < 0.05$ , 2-tailed). Sleep was more often punctuated by episodes of wakefulness after thymoxamine and in the time required to

accumulate the second, third and fourth hours of sleep there intervened a mean hourly  $0.3 \pm 0.5$  min of wakefulness on saline nights but  $5.5 \pm 7.1$  min on thymoxamine nights ( $t = 2.26$ , d.f. = 9,  $P < 0.05$ , 2-tailed). In hours 5-7 intervening wakefulness on saline amounted to  $1.2 \pm 1.2$  min, on thymoxamine  $0.9 \pm 1.9$  min (NS).

Apart from the periods of recording clearly classifiable as stage REM there were episodes on some thymoxamine nights of similar appearance except for retention of fairly high muscle tone and relatively sparse eye movements. This anomalous sleep stage was excluded from the above figures but averaged 0.8 min/h in hours 2-4.

Injections of thymoxamine appeared capable of provoking REM periods. Examining sleep cycle durations in terms of the time from the start of the first REM period to the start of the second REM period and then to the start of the third REM period, there were four cycles of between 30-36 min duration on thymoxamine nights and none on saline nights.

The blood pressure data were evaluated by comparing readings associated in time with the thymoxamine (30 mg) injection and those associated with the saline injection. The blood pressure reading just prior to each injection and the three immediately following each injection were selected, the mean of the two instances for each individual obtained, and then the group mean and standard error for each of the four blood pressure values. Figure 3 indicates that there was no difference between the saline and thymoxamine condition. A small rise from the time of the preliminary saline injection may have related to complaints of increasing discomfort from injections into the same arm and often the same vein.



**Figure 3** Blood pressures (mean  $\pm$  s.e. mean,  $n = 6$ ;  $\circ$  systolic;  $\bullet$  diastolic) (a) in the early part of the session in relation to the preliminary i.v. saline injection (b) in relation to thymoxamine (30 mg, i.v.) (c) in relation to saline i.v. (administered as often before as after thymoxamine) (d) at 25 and 30 min after the last injection. There is a slight rise overall but no difference between the two principal conditions.

## Discussion

The occasional anomalous REM-like sleep, in which muscle tone remained fairly high, has been seen not only in this study but in earlier ones in which drugs affecting brain amines were used (Akindele, Evans & Oswald, 1970; Dunleavy *et al.*, 1972).

Sabelli, Bartizal, Giardina & Myles (1972) found  $\alpha$ -adrenergic receptor blocking agents modified cortical visual evoked potentials in rabbits, and Rees, Butler, Gosling & Besser (1970)

found that thymoxamine altered the human pituitary hormone response to methylamphetamine. These observations and our own indicate that thymoxamine acts on the brain, including the human brain, and, by extended inference, that it does so through  $\alpha$ -adrenergic receptor blockade (Birmingham & Szolcsányi, 1965).

Our findings cannot be attributed to secondary effects through blood pressure changes and are consistent with beliefs that brain noradrenaline is involved in the regulation of sleep. Hartmann & Schildkraut (1973) proposed an inverse correlation between available brain noradrenaline and REM sleep duration. They pointed out that the amount of noradrenaline in the brain can be reduced either by the administration of  $\alpha$ -methylparatyrosine, with concomitant increase of REM sleep duration (Hartmann, Bridwell & Schildkraut, 1971; King & Jewett, 1971; Stern & Morgane, 1973; Wyatt, Chase, Kupfer, Scott, Snyder, Sjoerdsma & Engelman, 1971) or by 6-hydroxydopamine, also with increase of REM sleep (Hartmann, Chung, Draskoczy & Schildkraut, 1971). Using a different method we too have reduced available noradrenaline and, in harmony with the above authors' belief have observed REM sleep enhancement. Specifically our work links REM sleep control to  $\alpha$ -adrenergic receptor action but, more widely, suggests interdependent mechanisms for the control of slow wave sleep stages 3 and 4 and of sleep-wakefulness generally.

The research was supported by the Medical Research Council. Dr Thacore held a British Council Fellowship. We are indebted also to Professor Paul Turner, Helen Field, Jane Salmon, Barbara Bierer and Joe Palca; also to Dr J.M. McGilchrist of William R. Warner and Co. Ltd.

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## Brain rhythm that correlates with obesity

There is a strong correlation between an adult's body weight and usual amount of REM (rapid eye movement) (paradoxical) sleep.<sup>1</sup> I now report a connection between the degree of obesity and the frequency of an ultradian brain rhythm here measured during sleep but also present by day.<sup>2</sup> Sleep is categorised into two types, REM and NREM (non-rapid eye movement) (or orthodox), which alternate as sleep progresses. A cycle is made up of a period of NREM sleep plus an adjacent period of REM sleep and lasts about 100 minutes.

### Subjects, methods, and results

The sleep of 16 healthy adults (10 women and 6 men) aged 52 to 67 years (mean 59 years) was recorded electrophysiologically on six consecutive nights every four weeks during a 16-week period. They were weighed in light clothing on the first and sixth nights. The first night of each six was for adaptation only. Recordings were from 10.15 pm to 7 am. The length of each successive sleep cycle in each of the 320 records was computed as the minutes elapsing between the beginning of one period of NREM sleep and the end of the following period of REM sleep. Cycles containing over one minute of wakefulness were excluded. The average length of the first, second, and third cycles in each subject's 20 records was calculated and then the mean taken of the average of the first, second, and third cycles.

The mean of each subject's eight weight measures was calculated and his or her standing height measured. The ideal body weight for each subject's height<sup>3</sup> was subtracted from their mean measured weight and the deviation expressed as a percentage of the ideal body weight. The percentage deviation from ideal body weight was significantly correlated with the mean NREM-REM cycle length ( $r=0.563$ ,  $P<0.03$ , two-tailed) (figure), whereas mean body weight was not ( $r=0.164$ ; NS). The mean total minutes that subjects slept was also correlated with the percentage deviation from ideal body weight ( $r=0.536$ ,  $P<0.04$ , two-tailed), and with the mean sleep cycle length ( $r=0.572$ ,  $P<0.03$ , two-tailed).

### Comment

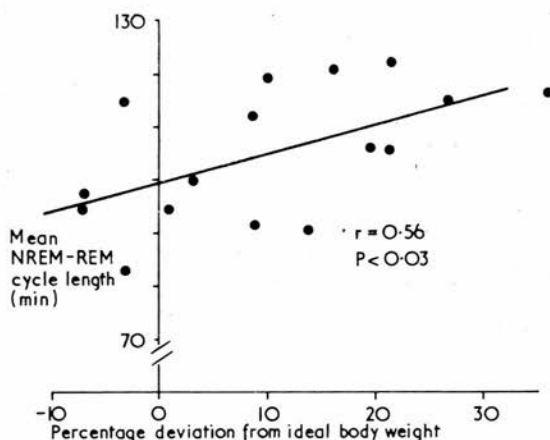
These findings give further evidence for a connection between metabolism and sleep and show an association between a fundamental brain rhythm and the degree by which a person is under or overweight. The correlation with sleep duration confirms the common belief that

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Correlation of percentage deviation from ideal body weight with mean NREM-REM cycle length in 16 adults.

fat people sleep more than thin people, and it agrees with the reported shortening of sleep in obese patients when they reduce weight<sup>4</sup> and the lengthening of sleep when anorexic patients regain weight.<sup>5</sup>

I thank Dr Ian Oswald and Beecham Products Ltd for their help.

<sup>1</sup> Adam, K, *British Medical Journal*, 1977, **1**, 813.

<sup>2</sup> Kripke, D F, in *Advances in Sleep Research*, ed E D Weitzman, vol 1. New York, Spectrum Publications, 1974.

<sup>3</sup> Metropolitan Life Insurance Company, *Statistical Bulletin*, 1960, **41**, February, p 6, March p 1.

<sup>4</sup> Crisp, A H, et al, *Psychotherapy and Psychosomatics*, 1973, **22**, 159.

<sup>5</sup> Lacey, J H, et al, *British Medical Journal*, 1975, **4**, 556.

(Accepted 29 March 1977)



## Body weight correlates with REM sleep

The fact that REM (rapid eye movement) (paradoxical) sleep is a time when dreaming occurs<sup>1</sup> has led to a neglect of somatic functions and to unsuccessful attempts to relate an individual's personality traits to his characteristic amount of REM sleep. To obtain a reliable measure of the latter it is important to allow adaptation to the sleep laboratory, to record a large number of nights, preferably consecutive, and to allow adequate time in bed each night.

### Methods and results

Sixteen healthy volunteers aged 52-67 (mean 59 years), six men and 10 women, slept in the laboratory every four weeks during a 16-week period and always did so for six consecutive nights, of which the first was for adaptation. Lights-out was from 2215 to 0700 h. At the start and end of each week of attendance they were weighed in light clothing. None of the volunteers were receiving drugs affecting the nervous system and they were asked to abstain from alcohol throughout. The 320 electrophysiological records were scored in terms of the usual international criteria. The amounts of each sleep stage on each night were calculated and also, for each subject, the means for his or her 20 nights. The means of the eight weight measures were also calculated.

It was found that body weight and the percentage of total sleep that was spent in REM sleep were related. Spearman's rank correlation test was employed and  $r_s = 0.774$ ,  $t = 4.57$ ,  $P < 0.001$ , 2-tailed. Log body weight was also correlated with mean total number of minutes of REM sleep (with a product-moment correlation,  $r = 0.643$ ,  $t = 3.07$ ,  $p < 0.01$ , 2-tailed). The figure illustrates the simple correlation between body weight and percentage of REM sleep. No correlations were found between body weight and total sleep, slow wave sleep or other sleep variables.

### Discussion

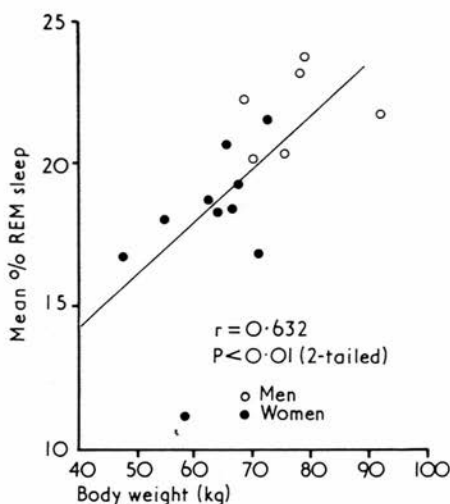
When patients with anorexia nervosa gained weight the most significant change in their sleep lay in an increase of REM sleep,<sup>2</sup> while in a study of acute starvation REM sleep fell significantly.<sup>3</sup>

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Simple correlation between body weight and percentage of REM sleep.

In rats the amount of REM sleep in a 12 h period accurately predicted food intake in the subsequent 12 h.<sup>1</sup> These observations are consistent with the present finding and since log body weight is highly correlated with the daily metabolic rate<sup>5</sup> it seems likely that REM sleep is closely linked to general body metabolism and restitution.

I would like to thank Dr Ian Oswald and Beecham Products Ltd for their help.

<sup>1</sup> *British Medical Journal*, 1976, **2**, 1523.

<sup>2</sup> Lacey, J H, *et al*, *British Medical Journal*, 1975, **4**, 556.

<sup>3</sup> MacFadyen, U M, Oswald, I, and Lewis, S A, *Journal of Applied Physiology*, 1973, **35**, 391.

<sup>4</sup> Siegel, J M, *Physiology and Behavior*, 1975, **15**, 399.

<sup>5</sup> Kleiber, M, *The Fire of Life: an Introduction to Animal Energetics*. New York, John Wiley and Sons, 1961.

(Accepted 10 December 1976)

## MESORIDAZINE AND HUMAN SLEEP

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- 1 Mesoridazine, a phenothiazine of short half-life, and potentially useful as an hypnotic, has here been investigated using volunteers of late middle age.
- 2 The electrophysiological recording of all-night sleep was studied in seven subjects for a 7-week period during which they received mesoridazine (10 mg nightly) for 3 weeks. The drug reduced the frequency of transitions into wakefulness and stage 1 (drowsiness) and reduced the time spent in stage 1; there was a withdrawal rebound. Mesoridazine increased REM sleep above baseline levels and a rebound fall below baseline occurred on withdrawal. The drug did not alter the amount of stage 3 + 4 slow wave sleep.
- 3 Subjective self-ratings were assessed in a 6-week study of sixteen subjects. Sleep quality improved on mesoridazine (10 mg nightly) but there was diminution of zest and freshness 20 min after rising. Daytime concentration and anxiety were rated as not affected either by administration or withdrawal.

### Introduction

Mesoridazine is a phenothiazine that has been used for some years in the treatment of psychoses. Its short half-life has led to employment as an hypnotic, mesoridazine 10 mg being found comparable to nitrazepam 5 mg in a clinical trial utilizing patients' judgements of sleep quality (Spiegel, 1973). Since phenothiazines have no reputation as drugs of dependence, further investigation of the hypnotic function was merited. We report a study of electrophysiological variables and of some subjective effects.

Single-night drug studies can be misleading: drugs taken clinically for long periods need to be evaluated in chronic laboratory studies. The labour and expense of these limit the number of subjects. Conventional statistical methods are ill-adapted to situations in which there is a gradual evolution of effects during weeks. This fact and small numbers of subjects can hamper statistical evaluation. Sometimes estimation of simple probability is useful (Oswald, 1973).

### Methods

Seven volunteers participated in the principal study with the agreement of their general practitioners and of the Ethics Committee of the Royal Edinburgh Hospital. There were four women aged 48-62 years, and three men, 52-60 years. None had taken CNS drugs in the preceding year. They took no alcohol during the study and

followed a regular way of life. Their physical health was satisfactory but, to enhance clinical relevance, they were chosen for their high incidence of personal problems, e.g. one had become a widow in the previous year and another had been divorced.

Each subject attended the laboratory on a total of nineteen nights, spread over 7 weeks. The intervals between nights were identical for all seven subjects. The plan of attendance was as follows:

Week	1	2	3	4
Laboratory	2 + 3	3	0	1 + 3
	Placebo	Drug	Drug	Drug
Week	5	6	7	
Laboratory	3	0	1 + 3	
	Placebo	Placebo	Placebo	

Where 1 + 3 or 2 + 3 are shown above, this means that there were one or two adaptation nights under full laboratory conditions preceding actual recording nights.

Mesoridazine (10 mg) in sealed capsules or matching blanks were taken at night about 10 min prior to lights-out throughout the whole period of the sleep study, and during the 2 preceding weeks.

Subjects slept in comfortable beds in ventilated, sound-attenuated rooms. Mid-line parieto-occipital electrodes recorded the electroencephalogram, two electrodes recorded submental electromyogram, and four electrodes above and below the outer



canthi recorded in bipolar and diagonal fashion the eye movements. Paper recording speed was 15 mm/second. Lights-out was 22.30 h till 07.15 h approximately. All records were ultimately coded, and then in random order were scored blind in terms of sleep stages (Rechtschaffen & Kales, 1968). The raw scores were processed by computer.

In statistical evaluation of the sleep data there were instances where simple probabilities indicated that chance could hardly provide an explanation, and elsewhere analysis of variance has been used. Preliminary *F*-tests had shown that the population variances under the different experimental conditions were not significantly different, so that parametric tests could justifiably be employed.

A computer programme carried out the arithmetic steps involved. From the variance ratio for each variable, with the degrees of freedom and standard *F*-distribution tables, *P* values were found. In some instances we have used mean values for data across the first 7 h of sleep of each subject and then the mean for that subject across the 3 nights in each phase of the experiment. Such a grouping for statistical purposes is conservative and fails to take account of changing trends, e.g. a rising trend during early drug withdrawal.

Subjects rated each evening their anxiety and their ability to concentrate during the preceding day, using 10 cm visual analogue scale previously described (Ogunremi, Adamson, Březinová, Hunter, MacLean, Oswald & Percy-Robb, 1973). Each morning, 20 min after rising they similarly rated their sleep quality and also their feelings of how full of zest and freshness they felt.

In the light of the results from the seven subjects of the initial experiment, a further study was undertaken of subjective ratings using sixteen subjects, aged 49-68, mean 58 years, eight men

and eight women. They received placebos for twenty nights, then mesoridazine (10 mg nightly) for fourteen nights, followed by placebos for seven nights.

## Results

In Tables 1 and 2 are presented data of principal interest. The study can be divided into five periods: baseline, early drug, late drug, early withdrawal, late withdrawal. Where in Table 1 means are given these are for all twenty-one subject-nights per period and for the first 7 h of accumulated sleep. In some instances, subjects did not sleep as long as 7 hours. While there were only four instances of nights where subjects slept less than 6 h, there were 25 out of 105 subject-nights where 7 h of sleep were not completed, spread fairly evenly across the conditions. The data for Table 1 have been arrived at by taking the mean number of minutes for each stage of sleep in the first hour of sleep, the mean for the second hour of sleep and so on, and then taking the sum of these means. Where there had, for example, been only 40 min sleep in the seventh hour of one subject, the mean for the seventh hour for the seven subjects was obtained through division by  $\frac{40}{60}$  or 6.67.

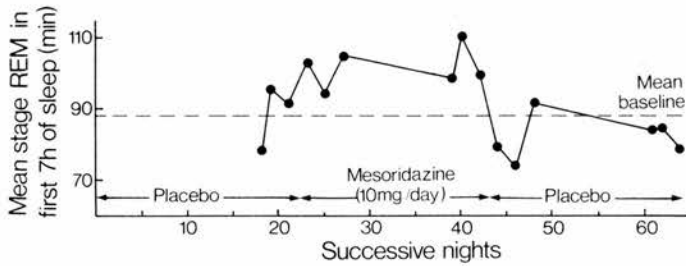
In general, mesoridazine (10 mg) did not greatly affect the normal pattern of sleep and where it did the effects did not markedly differ between the first three and the second three hours of sleep.

### REM sleep

The clearest influence of the drug was an increase in the duration of REM sleep, with a negative

**Table 1** Mean  $\pm$  s.e. mean results of variation in sleep time for twenty-one subject-nights per period for the first 7 h of accumulated sleep after mesoridazine (10 mg)

	Period				
	Baseline	Early drug	Late drug	Early withdrawal	Late withdrawal
REM sleep (min)	88.2 $\pm$ 5.3	100.4 $\pm$ 5.1	103.0 $\pm$ 9.2	81.4 $\pm$ 4.8	82.3 $\pm$ 11.0
Stage 3 + 4 (min)	70.5 $\pm$ 17.4	64.2 $\pm$ 17.3	66.0 $\pm$ 16.1	61.3 $\pm$ 17.5	36.6 $\pm$ 7.5
Stage 1 (min)	45.0 $\pm$ 13.8	42.0 $\pm$ 12.1	42.1 $\pm$ 9.6	49.7 $\pm$ 15.4	49.0 $\pm$ 10.2
Shifts to stage 1 & awake	45.5 $\pm$ 9.7	40.1 $\pm$ 7.8	41.1 $\pm$ 7.8	53.0 $\pm$ 12.2	53.8 $\pm$ 10.8



**Figure 1** REM sleep duration is higher during mesoridazine intake. A rebound fall is present with the lowest out of the fifteen values being present on the second recorded withdrawal night (actually the third withdrawal night).

rebound, most marked on the second recorded withdrawal night (the third actual night of withdrawal). The means for all six drug nights are higher than the means of eight out of nine of the non-drug nights (Figure 1). The probability of such a difference occurring by chance is remote. On analysis of variance the means for the early drug week were significantly greater than baseline ( $F = 6.05$ ; d.f. 1,6;  $P < 0.05$ ) and the means for the first withdrawal week lower than for the late drug week ( $F = 9.15$ ; d.f. 1,6;  $P < 0.05$ ).

Six of the seven subjects had higher early drug means than baseline means. The mean of the three early withdrawal nights was lower than the baseline mean for six of the seven subjects.

#### Stage 3 + 4 sleep

As is common in this age group, there were two subjects who had very little of stages 3 and 4 sleep. Tables 1 and 2 indicate that the sustained use of the drug did not suppress stage 3 + 4 sleep during the period of drug administration. In the third withdrawal week there are lower mean values, and,

indeed, analysis of variance indicated significantly lower values than baseline ( $F = 6.63$ ; d.f. 1,6;  $P < 0.05$ ), but two subjects had higher individual means.

#### Time in stage 1 (drowsiness)

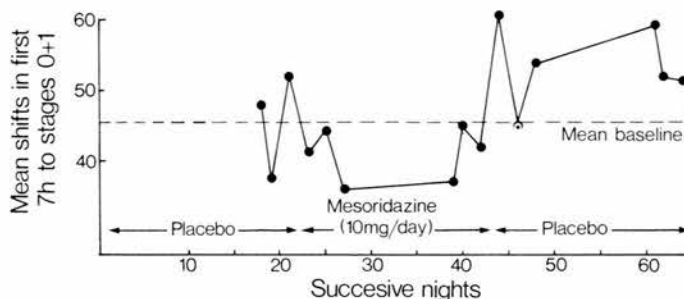
The proportion of sleep spent in stage 1 after first sleep onset tended to be less during the period of the drug administration (Table 1). Among the 15 nights, the three lowest means were all during the drug period. The highest mean value occurred on the second recorded withdrawal night and values tended to remain high throughout the post-drug period.

#### Intra-sleep restlessness

Frequency of shifts into stage 1 sleep or wakefulness from any other stage of sleep fell, as Table 1 and Figure 2 show, all six means during drug administration lying below the baseline mean. A rebound followed withdrawal. Analysis of variance confirmed the significance of the early

**Table 2** Mean  $\pm$  s.e. mean results for variation in sleep time and pattern after mesoridazine (10 mg)

	Period				
	Baseline	Early drug	Late drug	Early withdrawal	Late withdrawal
Total sleep time (min)	443.3 $\pm$ 20.6	453.0 $\pm$ 14.6	446.3 $\pm$ 15.6	436.4 $\pm$ 15.4	444.2 $\pm$ 11.2
Sleep onset latency (min)	47.6 $\pm$ 15.2	42.4 $\pm$ 8.6	48.4 $\pm$ 10.6	27.6 $\pm$ 6.3	28.3 $\pm$ 5.2
% REM (whole night)	21.3 $\pm$ 1.4	24.3 $\pm$ 1.6	24.4 $\pm$ 1.8	19.5 $\pm$ 1.2	21.3 $\pm$ 2.5
% Stage 3 + 4 (whole night)	14.1 $\pm$ 3.8	14.6 $\pm$ 3.9	15.7 $\pm$ 4.0	13.6 $\pm$ 3.8	8.4 $\pm$ 1.7



**Figure 2** Intra-sleep restlessness has its lowest values during drug administration and is highest on the first withdrawal night.

withdrawal rise compared with baseline ( $F = 6.82$ , d.f. 1,6;  $P < 0.05$ ) and with the late drug period ( $F = 6.00$ , d.f. 1,6;  $P < 0.05$ ). Every one of the seven subjects had higher means scores for restlessness in the early withdrawal period compared with the late drug period. The increase was most apparent on the first withdrawal night, when the group mean was the highest among the 15 nights.

#### *Sleep duration*

Mean total sleep duration was greatest on the first drug night and least on the first withdrawal night but the variance was high.

#### *Sleep onset latency*

There was a high variance in the delay to falling asleep and mesoridazine (10 mg) taken immediately prior to lights-out did not have an obvious effect, and nor did its withdrawal (Table 2).

#### *Intervening wakefulness*

There was a high variance in the degree to which sleep was broken. Where, for example, one man lies awake for 249 min in the middle of one night, the numerical data are distorted. Table 1 indicates no clear drug effect. As with stage 1 duration, however, the values are high after withdrawal.

#### *REM sleep latency*

This measure is normally bimodal and means are inappropriate. The incidence of short latencies after withdrawal is usually of interest. Latencies under 45 min were: two among all 63 non-drug nights and 5 among 42 drug nights.

#### *NREM-REM cycle*

The mean cycle duration across each night for each individual was determined by the method of Bržinová (1974). Overall mean durations and s.e. mean were: baseline  $98.5 \pm 4.9$  min, early drug week  $96.2 \pm 4.4$ , late drug week  $99.8 \pm 6.4$  min, early withdrawal week  $101.2 \pm 3.1$  min and late withdrawal week  $90.3 \pm 5.3$  min. Analysis of variance did not reveal any significant differences.

#### *REM profusion*

Sample counts were made of the number of 2-s epochs containing rapid eye movements in the third and fourth REM periods of the nights. The first 5 min of each period was excluded and the counts covered the 5.33 min thereafter. Mean counts and s.e. mean were  $99.0 \pm 8.5$  for baseline,  $95.8 \pm 14.0$  early drug week and  $89.0 \pm 19.1$  for early withdrawal week. The variance was high and there was no indication of change induced by the drug.

#### *Subjective ratings*

The initial study of seven subjects provided hypotheses for the later study of sixteen subjects. In the initial experiment mesoridazine improved the subjective quality of sleep throughout administration, with mild impairment immediately after withdrawal. Figure 3 reveals that this was confirmed in the sixteen-person study and in the statistical evaluation the last two baseline placebo weeks were compared with the two mesoridazine weeks using repeated measures analysis of variance (Winer, 1962) and the difference was found to be significant ( $F = 12.45$ ; d.f. 1,420;  $P < 0.001$ ).

Twenty minutes after rising from bed subjects rated themselves as more sleepy and lack-lustre in



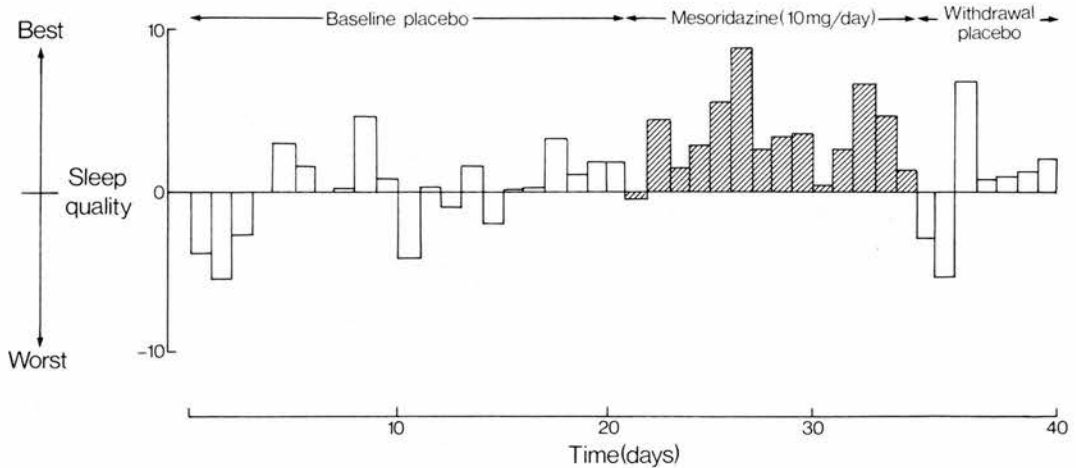


Figure 3 Sleep quality is subjectively improved by mesoridazine. Shown are daily means for sixteen subjects of the deviation from the individual's own baseline mean.

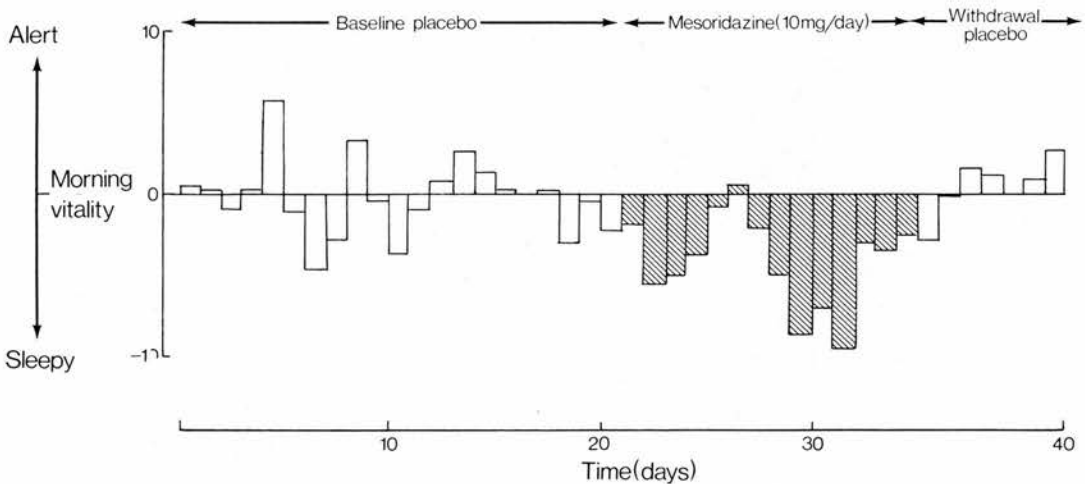


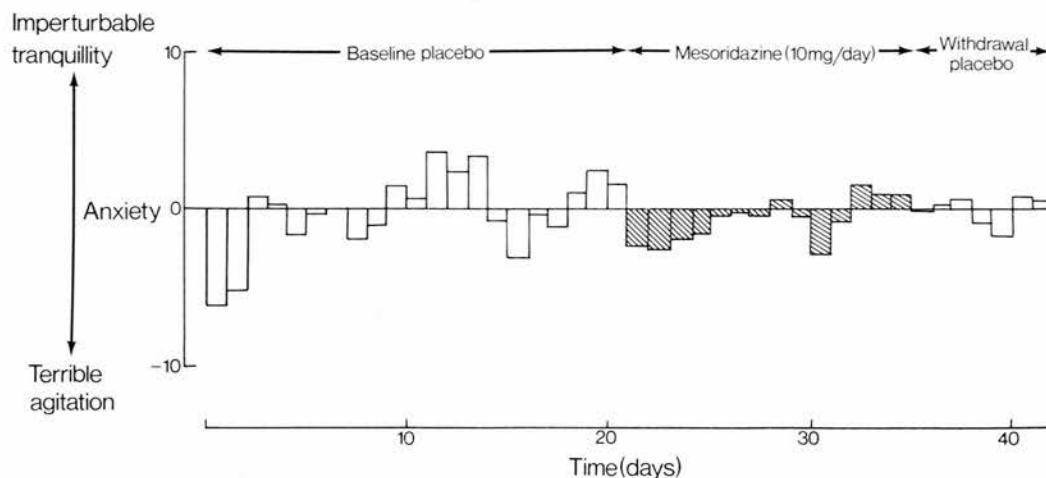
Figure 4 Morning vitality is rated poorer after mesoridazine. Shown are daily means for sixteen subjects of the deviation from the individual's own baseline mean.

both the initial study and in the sixteen-person study as Figure 4 reveals. Again analysis of variance revealed a significant difference ( $F = 24.826$ ; d.f. 1,420;  $P < 0.001$ ). Nevertheless evening ratings of how well it had been possible to concentrate throughout the day suggested impairment only on the first day in the initial study and in the sixteen-person study no marked or consistent effect of mesoridazine was detected.

There was no effect of the drug on self-rated anxiety either during administration or withdrawal (Figure 5).

#### Discussion

In comparison with the many reports of the effects of hypnotic drugs on sleep, two features of



**Figure 5** Lack of effect of mesoridazine on daytime anxiety. Shown are daily means for sixteen subjects of the deviation from the individual's own baseline mean.

the present EEG study are of note. There was no sign of reduction in slow wave sleep, stages 3 + 4, during chronic intake, contrasting particularly with benzodiazepines such as flurazepam (Kales, Allen, Scharf & Kales, 1970; Kales, Kales, Scharf & Tan, 1970; Kales & Scharf, 1973; Dement, Zarcone, Hoddes, Smythe & Carskadon, 1973), diazepam (Kales & Scharf, 1973), chlor-diazepoxide (Hartmann & Cravens, 1973), and flunidazepam (Kales & Scharf, 1973; Oswald, Lewis, Tagney, Firth & Haider, 1973). Whereas REM sleep duration is reduced by most hypnotics, mesoridazine caused an increase above normal of REM sleep duration, consistent with which was a rebound fall below baseline after withdrawal.

Also notable was the lack of effect on self-rated daytime anxiety and especially the absence of withdrawal-induced anxiety, which contrasts sharply with the withdrawal anxiety found in a similar study of a benzodiazepine hypnotic (Allen & Oswald, 1975).

The decrease of intra-sleep restlessness, of time in stage 1, and the subjective improvement of sleep quality with mesoridazine were all as expected of an hypnotic and the reverse changes during the withdrawal period are consistent and customary. The low mean values for stages 3 + 4 in the late withdrawal period do not conform to any prediction, and the inconsistency among subjects suggests chance as an explanation.

The phenothiazines as a class are believed to interfere with catecholamine action and, in man,

both chlorpromazine and thioridazine (of which mesoridazine is a metabolite) lead to receptor blockade for noradrenaline (Tuck, 1973). Arguing from animal experiments Hartmann & Schildkraut (1973) proposed an inverse correlation between available brain noradrenaline and REM sleep duration, and we too have found that in man the alpha adrenergic blocking agent, thymoxamine, given intravenously, increased REM sleep duration (Oswald, Thacore, Adam, Bržinová & Burack, 1975). Earlier evidence indicating that chlorpromazine may increase REM sleep (Lewis & Evans, 1969), together with the present finding with mesoridazine, are thus consistent with the Hartmann and Schildkraut hypothesis.

The biological importance of altered proportions of electrophysiologically-defined sleep stages is uncertain but some significance is currently attached to stage 3 + 4, and to REM sleep. The large nocturnal release of growth hormone depends upon the occurrence of stages 3 and 4 sleep in undrugged persons (Sassin, Parker, Johnson, Rossman, Mace & Gotlin, 1969; Schnure, Raskin & Lipman, 1971). The fact that mesoridazine does not cause suppression suggests it would not interfere with the secretion of growth hormone, the anabolic action of which presumably assists in sleep's restorative role. REM sleep is tentatively seen as a time especially important for synthetic and repair processes in the brain (Oswald, 1969, 1970; Hartmann, 1973; Stern & Morgane, 1974) and hypnotic drugs that reduce

this stage of sleep might be thought undesirable: conversely the slight increase of REM sleep caused by mesoridazine might be of merit.

When coupled with the low abuse potential of phenothiazines, mesoridazines's lack of effect on anxiety, its lack of effect on stage 3 + 4 sleep and

its enhancement of REM sleep, would make the drug appear worthy of further serious consideration.

We are indebted to Dr V. Březinová and Miss Anne Hogg for assistance.

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## Subjective ratings of sleep quality and anxiety after placebo, drug and a food drink

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### Summary

Ten subjects (mean age 57 years) took part in a cross-over study between a food drink and nitrazepam 5 mg. They rated their anxiety and sleep quality. On half the sleep laboratory nights during baseline periods subjects were given an inert pill which they were told would improve sleep. A comparison was made between the six pill and six non-pill nights for each subject. Subjective ratings revealed no significant difference attributable to the inert pill. Sleep quality was rated to have been improved during both late drug and early food drink administration. On early drug withdrawal sleep quality was rated worse than baseline.

### Introduction

There have been very few studies of the effect of placebo on sleep, and yet this is an important consideration when a treatment is administered whose nature cannot be disguised, and with which subjects may associate an effect. In a study comparing placebo, flurazepam and no treatment, Kales *et al.* (1971) demonstrated no effect of placebo on sleep induction, maintenance, stages or on subjective assessment of sleep quality. Davis and Hartmann (1973) recorded subjects electrophysiologically and found no significant difference in total sleep time and sleep onset latency between the means of three placebo and three treatment nights. In a later experiment, comparing the EEG recordings of subjects on placebo for 28 days with a preceding baseline period, Hartmann and Cravens (1973) believed they had found a rather tenuous connection between placebo administration and an increased amount of REM sleep which continued into early withdrawal from placebo. The present study differs from those mentioned above in that our subjects were told that the inert pill would have a beneficial effect on their sleep and hence more specifically investigated the power of suggestion.

### Methods

Ten healthy subjects aged 41-62 years (mean 57 years) took part in a cross-over study between a food drink and nitrazepam 5 mg.

Subjects attended the sleep laboratory in pairs differing from each other for the experimental condition. Each subject slept in quiet and comfortable conditions on a total of 58 nights spread over 38 weeks according to the experimental design in Table 1.

TABLE 1. The experimental design used

Week No.	Treatment
1 and 2	2 Adaptation nights 6 Baseline nights
5 and 6	1 Adaptation night 6 Early treatment nights
7, 8, 9 and 10	Treatment continued at home
11 and 12	1 Adaptation night 6 Late treatment nights
13 and 14	Treatment continued at home
15 and 16	1 Adaptation night 6 Withdrawal nights

Six weeks later, subjects repeated the above schedule on the alternative treatment. Treatments were administered about 30 min before lights out (approximately 10.30 p.m. to 7.30 a.m.).

Subjects rated their own sleep quality in the morning and in the evening rated their daytime anxiety using visual analogue scales (0-100 mm) where sleep quality ranges from 'worst' to 'best' and anxiety from 'terrible agitation' to 'imperturbable tranquillity'.

On half the baseline nights and in balanced order each subject was given a pink placebo pill. They were told that these would 'help make your sleep more restful without causing any hangover'. The food

drink was made with 32 g of Horlicks powder mixed with 250 ml of hot milk. The drug and the food drink were each taken for 10 weeks by every subject.

## Results

Ignoring the subjective ratings collected on the adaptation nights, each of the ten subjects had a total of twelve baseline nights (six pill and six non-pill) and six laboratory nights for each of the other experimental conditions.

Friedman's analysis of variance (Siegel, 1956) of the subjective ratings from both baseline periods demonstrated that when the inert pill had been taken the night before neither sleep quality improved ( $\chi^2 = 3.45$ , d.f. = 3, n.s.) (Table 2) nor anxiety altered ( $\chi^2 = 1.32$ , d.f. = 3, n.s.) (Table 4).

TABLE 2

Subjective sleep quality	mean $\pm$ s.e. (in mm)
Mean baseline: pill	45.6 $\pm$ 2.4
non-pill	49.2 $\pm$ 3.3 n.s.
	47.4 $\pm$ 2.6

TABLE 3

Subjective sleep quality	mean $\pm$ s.e. (in mm)
Mean baseline	47.4 $\pm$ 2.6
Early drug	50.1 $\pm$ 2.9
Late drug	53.0 $\pm$ 3.0†
Drug early withdrawal	39.9 $\pm$ 3.0*
Early food drink	50.7 $\pm$ 2.7†
Late food drink	49.8 $\pm$ 2.3
Food drink early withdrawal	50.7 $\pm$ 2.6

\* significantly lower than baseline at  $P < 0.05$  level (1-tailed test)

† significantly greater than baseline at  $P < 0.025$  level (1-tailed test)

Sleep quality was rated to have been improved during both the late drug ( $t = 2.28$ ,  $P < 0.025$ , 1-tailed) and early food drink ( $t = 2.63$ ,  $P < 0.025$ , 1-tailed) administration, when correlated  $t$ -tests were used to compare them with baseline (Table 2).

A difference between subjective ratings of sleep quality was seen when comparing the baseline mean

TABLE 4. Subjective anxiety ratings for the day before and the day following a night spent at the sleep laboratory

Mean $\pm$ s.e. (in mm)	
Before	
Mean baseline: pill	51.8 $\pm$ 1.8
non-pill	52.9 $\pm$ 2.1 n.s.
After	
Mean baseline: pill	52.7 $\pm$ 1.9
non-pill	51.2 $\pm$ 1.7 n.s.

with early withdrawal (laboratory nights 1, 2 and 3) from the drug, i.e. sleep being rated worse after drug withdrawal ( $t = 1.88$ ,  $P < 0.05$ , 1-tailed).

No significant differences were found between the baseline anxiety rating and any subsequent treatment.

## Discussion

Any experiment which sets out to investigate the value of a treatment whose identity cannot be concealed is faced with the problem of how big a part suggestion may play in the results. In this experiment subjects were specifically told that their sleep would be improved and yet this was not reflected in the subjective ratings. The results of the EEG sleep recordings made on the nights when subjects attended the laboratory appear also unaffected by placebo but will be reported at a later date.

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# Do placebos alter sleep?

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## Summary

Deliberate suggestion that an inert capsule was a sleeping pill was found not to influence subjective ratings of sleep quality or anxiety or the electrophysiologically recorded features of sleep in 10 volunteers aged 41-62 years.

## Introduction

Efforts are being made to persuade doctors to prescribe fewer sleeping pills. It is often asked whether an inert substitute might be effective through suggestion alone. Kales *et al*<sup>1</sup> compared the effect of placebo with that of no treatment in eight young men with complaints about their sleep and found no difference in objective measurements—delay to falling asleep, duration of sleep, or distribution of sleep stages—or in subjective ratings of sleep. Hartmann *et al*,<sup>2,3</sup> in two studies, also found no clear effects. Their proposed relationship between placebo administration and an increased amount of rapid-eye-movement (REM) sleep may have been an artefact of unbalanced design.

We here report the results of a further study in which 10 volunteers were given a placebo disguised as a sleeping pill.

## Patients and methods

The 10 volunteers, six women and four men, were aged 41-62 (mean 57) years. This age and sex distribution is representative of patients who most often complain of inadequate sleep. They were asked to keep to a regular daily routine and to take no drugs or alcohol.

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The volunteers were given the following written statement: "You will be given a mild sleeping pill; it will help to make your sleep more restful without causing any hangover." An inert pink pill was given 30 minutes before lights-out on half of the recorded nights. The volunteers attended the laboratory in pairs, only one of them receiving the pill on any one night. The experiment was divided into two periods of two weeks separated by 21 weeks. During each period the volunteers attended for electrophysiological recording on eight nights, the first two serving for adaptation. Thus each person received the pill on six nights and nothing on another six nights, the order being balanced.

The electroencephalogram (EEG), eye movements, and submental muscle tone were recorded from 22.30 until 07.15. The recordings were categorised<sup>1</sup> by a scorer who was unaware of the experimental condition, and the sleep and wakefulness data then analysed for their mean accumulation in minutes after one hour, two hours, and so on up to seven hours of sleep.

Each evening the volunteers rated their average anxiety for the day, and each morning rated their sleep, using 10 cm visual analogue scales. The scales ranged from "terrible agitation" to "imperturbable tranquillity," and from "the worst" to "the best night imaginable." Correlated *t* tests were used to compare the 60 placebo nights and 60

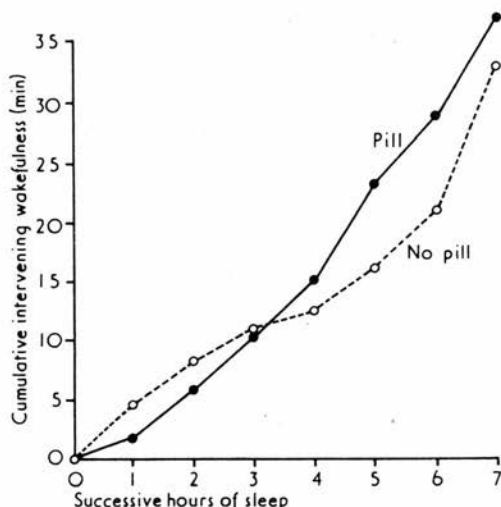


FIG 1—Mean cumulative minutes of wakefulness during night's sleep of 10 volunteers on pill nights and no-treatment nights ( $t=0.90$ ;  $DF=9$ ; NS).

no-treatment nights using each person's mean score under each condition.

## Results

The subjective ratings showed no change in sleep quality when the pill nights were compared with the no-treatment nights (mean

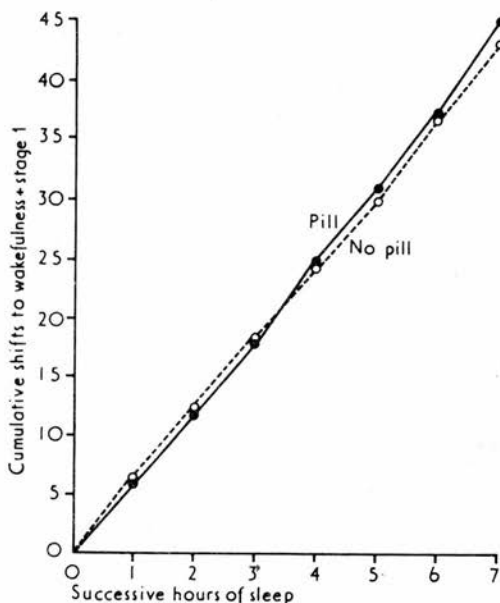


FIG 2—Mean combined numbers of times that sleep was disrupted by wakefulness and periods of drowsiness (stage 1) in the 10 volunteers on pill nights and no-treatment nights.

scores ( $\pm$  SE of mean)  $45.6 \pm 2.4$  mm *v*  $49.2 \pm 3.3$  mm; NS). The volunteers knew when it was their turn to be given the placebo, but on the days when they were to take it at night their ratings of anxiety were not altered ( $51.8 \pm 1.8$  mm *v*  $52.9 \pm 2.1$  mm; NS).

The electrophysiological recordings showed no significant differences between the 60 pill nights and the 60 no-treatment nights. This was true for the mean time it took to fall asleep ( $24.9 \pm 3.9$  min *v*  $21.9 \pm 4.2$  min; NS) and for the accumulation of wakefulness that intervened during the night's sleep or any of its parts (fig 1). The amounts of stage 1 (drowsiness), stage 2, stages 3 and 4, and REM sleep, total sleep duration, and REM sleep latency were similarly unaffected. The numbers of times that sleep was disrupted by waking or periods of drowsiness were combined and also found to be unaffected (fig 2).

## Discussion

The absence of any difference between the subjective ratings under the two conditions was not a result of insensitivity of the method. The same 10 volunteers had taken part in a cross-over study of nitrazepam 5 mg and a food drink. Their ratings showed a significant improvement in sleep quality for both substances, with a deterioration on withdrawal of the drug.<sup>5</sup>

In older people sleep is frequently broken by periods of wakefulness<sup>6,7</sup> and is thus likely to show any influence of a

sedative. In a study of a food drink (Horlicks) no significant effect was found on EEG-recorded sleep of young people, whereas the sleep of a group of older people similar to those studied here became significantly less broken than when a placebo pill was given.<sup>8</sup> After our report on Horlicks it was proposed that suggestion could have been responsible.<sup>9</sup> Our present studies offer no support for this, nor for any belief that when a placebo is prescribed for those of later middle age sleep will be substantially altered.

We thank Beecham Products Ltd for their help.

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# Nitrazepam: lastingly effective but trouble on withdrawal

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*British Medical Journal*, 1976, 1, 1558-1560

## Summary

The sleep of 10 volunteers with an average age of 57 years was recorded electrophysiologically before, during, and after nitrazepam 5 mg nightly for 10 weeks. Sleep was longer and less broken on the drug and no tolerance was obvious after two months' use. Withdrawal of the drug, however, caused sleep to be temporarily worse than before the drug had been taken. Slow-wave sleep was reduced by nitrazepam, but the accompanying secretion of growth hormone was not impaired.

## Introduction

We recently described how a placebo had no effect on sleep<sup>1</sup>; here, using the same 10 middle-aged volunteers, we report on the actions of nitrazepam 5 mg. We also looked for any influence on the nocturnal secretion of growth hormone (GH).

All-night electrophysiological recording makes precise measurement of the amount of time a person is asleep possible. It also shows two different kinds of sleep that alternate through the night. One is rapid eye movement (REM) or paradoxical sleep, the other is non-REM or orthodox sleep. The latter is subdivided into stages 1, 2, 3, and 4. Stages 3 and 4 are known as slow-wave sleep (SWS) and during these stages the large nocturnal secretion of GH occurs. In the undrugged condition the secretion depends on the presence of stages 3 and 4 and does not take place if these stages are not allowed to develop.<sup>2,3</sup> Growth hormone is thought to be important for sleep's restorative

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function, and since many benzodiazepines will reduce SWS, it seemed important to find out whether nitrazepam would impair GH secretion. In clinical practice drugs are taken for long periods, and so we conducted a study over many weeks.

## Methods

Ten volunteers, with the agreement of their general practitioners, took part in this study of nitrazepam 5 mg nightly. There were six women and four men aged 41-62 (mean 57) years. They had taken no drugs in the preceding months and were asked not to take any drugs other than those given by us and to consume no alcohol. Subjects attended the laboratory, to sleep in quiet and comfortable bedrooms according to the experimental design:

Weeks 1 and 2 ..	..	2 Adaptation nights, 6 baseline nights
Weeks 5 and 6 ..	..	1 Adaptation night, 6 early drug nights
Weeks 7 to 10 ..	..	Drug continued at home
Weeks 11 and 12 ..	..	1 Adaptation night, 6 late drug nights
Weeks 13 and 14 ..	..	Drug continued at home
Weeks 15 and 16 ..	..	1 Adaptation night, 6 withdrawal nights

The drug was taken 30 minutes before lights-out (about 2230 to 0715). On all nights the electroencephalogram, eye movements, and submental muscle tone were recorded.

Seven of the volunteers attended the laboratory for six additional nights, when blood was sampled through a catheter without disturbing the sleeper.<sup>4</sup> The six nights represented one adaptation night followed by one recording and blood sampling night during the baseline period and similarly one adaptation and one measurement night in the early drug phase and one adaptation and one measurement night in the late drug period. The blood samples were taken every 30 minutes, and the plasma was separated and stored deep-frozen until assayed.

The GH concentration in each sample was assayed "blind" as to the experimental condition by the MRC Radioimmunoassay Team in Edinburgh using the method of Hunter.<sup>5</sup> The GH results were expressed as mU/l (in terms of human growth hormone international reference preparation 66/217) concentration at the clock time when the blood sample was taken. These clock times were then converted, for each night, into time in minutes after the first onset of sleep. Graphs were plotted, and the area under the GH curve, from sleep onset to six hours later, was measured by a planimeter in cm<sup>2</sup>. The vertical scale was 1 cm/2 mU/l and the horizontal scale was 2 cm/hour.

The electrophysiological recordings were coded and categorised "blind" into the different stages of sleep and wakefulness.<sup>6</sup> The time it took subjects to fall asleep, the total amount of time they slept, and the hourly distribution and total number of minutes after the onset of sleep that they were awake and in each of the sleep stages were calculated.

STATISTICS—Friedman's analysis of variance was used to test the overall significance of the results,<sup>7</sup> and *t* tests for paired observations were used to compare the different periods of the experiment.<sup>8</sup>

## Results

The volunteers slept longer while taking the drug. This improvement in sleep was maintained throughout the drug period, but on

withdrawal from the drug the time spent asleep was significantly shorter than before the drug had been taken (table I).

TABLE I—Total time asleep in 10 subjects during six nights in each condition

Condition*	Mean ( $\pm$ SE of mean) time asleep (min)	Compared with baseline (Df = 9)
Baseline	446.9 $\pm$ 10.8	
Early drug	471.0 $\pm$ 7.9	$t = 2.50$ ; $P < 0.025$ , one-tailed
Late drug	469.1 $\pm$ 8.5	$t = 2.97$ ; $P < 0.01$ , one-tailed
Withdrawal	428.7 $\pm$ 12.9	$t = 2.61$ ; $P < 0.025$ , one-tailed

\*Overall significance of differences among conditions: Df = 3;  $\chi^2_r = 20.04$ ;  $P < 0.001$ .

Intervening wakefulness was still significantly reduced after eight weeks of nitrazepam administration (Df = 9;  $t = 1.83$ ;  $P < 0.05$ , 1-tailed) (fig 1). A similar reduction had been present during the early drug period (Df = 9;  $t = 2.25$ ;  $P < 0.05$ , 1-tailed), and the early and late drug periods did not differ significantly from each other. Withdrawal from the drug increased intervening wakefulness when compared with baseline values, (fig 1). We used the means for each hour, in so far as such data was available, but the fact that sometimes total sleep was very much reduced (in one case to 42 minutes) made statistical assessment of these particular data impracticable.

The amount of time awake, between first falling asleep and before lights-on in the morning, was significantly higher during the withdrawal period and considerably higher two nights after the last dose of

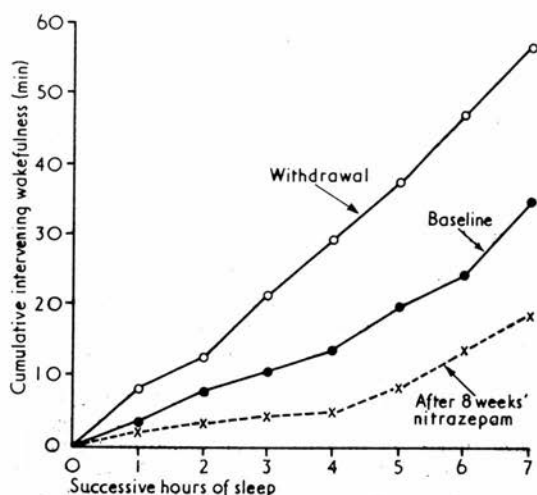


FIG 1—Mean cumulative minutes of wakefulness intervening during the sleep of 10 volunteers.



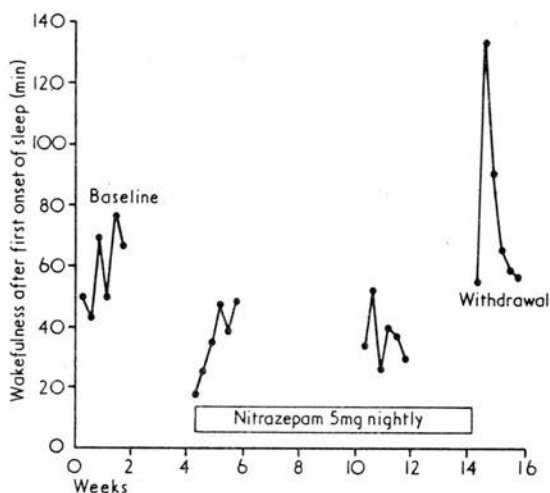


FIG 2—Mean total wakefulness recorded after first onset of sleep in 10 subjects. Overall significance of difference among four conditions:  $\chi^2 = 19.17$ ; Df = 3;  $P < 0.001$ .

Baseline *v* early drug: Df = 9;  $t = 3.24$ ;  $P < 0.01$  (1-tailed).

Baseline *v* late drug: Df = 9;  $t = 3.50$ ;  $P < 0.005$  (1-tailed).

Baseline *v* withdrawal: Df = 9;  $t = 1.87$ ;  $P < 0.05$  (1-tailed).

nitrazepam (fig 2). The time it took subjects to fall asleep was not significantly changed.

During the early drug period reduction in REM sleep occurred almost exclusively within the first three hours of sleep. This significant early night reduction was still present in the late drug period. As table II shows, however, by the late drug period a significant increase in REM sleep had appeared in the later night (hours 4-7 of sleep).

TABLE II—Total REM sleep (minutes) accumulated in successive hours of sleep in 10 volunteers. Results are means  $\pm$  SE of mean

Condition	Early night (1-3 hours)	Late night (4-7 hours)	First 7 hours of sleep
Baseline	26.2 $\pm$ 3.3	59.3 $\pm$ 3.5	85.5 $\pm$ 5.3
Early drug	16.3 $\pm$ 2.6†	58.5 $\pm$ 2.9	74.8 $\pm$ 4.6†
Late drug	18.6 $\pm$ 2.8*	65.8 $\pm$ 2.9*	84.4 $\pm$ 5.1
Withdrawal	26.5 $\pm$ 2.6	57.0 $\pm$ 3.7	83.5 $\pm$ 5.8

\*Significant difference from baseline,  $P < 0.05$  (2-tailed).

†Significant difference from baseline,  $P < 0.01$  (2-tailed).

The mean duration of SWS accumulated in the first six hours of sleep (table III) was significantly reduced during early and late drug administration when compared with baseline levels. The mean values recorded during the late drug period were significantly lower than those of the early drug period (Df = 9;  $t = 2.40$ ;  $P < 0.05$ , 2-tailed). There was a return to baseline levels during the withdrawal period.

During drug administration, however, there was no associated decline in GH secretion, but rather a tendency for higher (not significant) levels during drug administration. Friedman's non-parametric analysis of variance by ranks was used to compare the areas under the growth hormone curves. The mean areas ( $\pm$  SE of mean) under the growth hormone curves were: baseline  $9.3 \pm 1.7$  cm<sup>2</sup>; early drug  $12.3 \pm 2.6$  cm<sup>2</sup>; late drug  $18.3 \pm 4.8$  cm<sup>2</sup> ( $\chi^2_r = 3.71$ ; Df = 2; not significant).

TABLE III—Total SWS in first six hours of sleep in 10 volunteers

Condition*	Mean ( $\pm$ SE of mean) SWS (min)	Compared with baseline (Df = 9)
Baseline	79.0 $\pm$ 10.5	
Early drug	61.3 $\pm$ 10.7	$t = 4.22$ ; $P < 0.01$ , 2-tailed.
Late drug	49.9 $\pm$ 10.6	$t = 4.34$ ; $P < 0.01$ , 2-tailed
Withdrawal	72.7 $\pm$ 10.0	$t = 1.42$ ; not significant

\*Overall significant difference among conditions: Df = 3;  $\chi^2_r = 14.88$ ;  $P < 0.005$ .

## Discussion

As we grow older, we sleep less, and sleep is more broken by periods of wakefulness<sup>9-12</sup> and, perhaps as a consequence, there is an age-related increase in the consumption of sleeping pills.<sup>13</sup> Our volunteers were of an older age group and representative of patients who most often complain of inadequate sleep. The maintenance of nitrazepam's action in still reducing the amount of wakefulness after two months of use is paralleled by that of flurazepam when studied during two weeks of drug administration, but contrasts with the diminishing effectiveness of chloral hydrate (1000 mg) or glutethimide (500 mg).<sup>14</sup> The longer drug-taking period in our study was more likely to show any tolerance effects.

We found that nitrazepam reduced the amount of REM sleep in the first three hours of sleep and that, during chronic administration, a late-night REM sleep rebound developed. This REM sleep rebound in the later night during protracted use of hypnotics has been reported for barbiturates.<sup>15</sup> The lack of REM sleep rebound after withdrawal contrasts with that which is present after larger doses.<sup>16,17</sup>

The decrease in the amount of SWS has been found during chronic intake of other benzodiazepines—for example, flurazepam,<sup>13</sup> chlordiazepoxide,<sup>18</sup> diazepam,<sup>19</sup> and fosazepam.<sup>20</sup> The lack of any associated decrease in the blood level of GH suggests that the metabolic functions associated with SWS may not be impaired by nitrazepam administration.

The poor sleep caused by stopping nitrazepam is a further reminder of how such drugs create conditions that lead to perpetuation of intake. Patients should be told that after giving up nitrazepam 5 mg or similar drugs they may experience an increase in wakefulness for a week or two, with one or two nights of little sleep. They should be reassured that this disrupted sleep

is a temporary consequence of their dependence on the drug that has been withdrawn and that as the weeks pass their sleep will improve again.

We thank Beecham Products Ltd for their help.

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## **Sleep is for Tissue Restoration**

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It is traditionally believed that sleep helps children grow and that it restores us after a hard day. The belief is now supported by some 50 reports showing that rates of protein synthesis or of mitotic division are higher at the time of rest and sleep, though in man it has only been well established for the most accessible of tissues, the skin (Fisher, 1968).

Medical thinking has not yet grasped that tissue healing may be accelerated by sleep. There persists an assumption that degradation and synthesis in tissues not only continue all the time (as they do) but that they are continually equal (which they are not), and upon this invalid assumption has rested much clinical research into protein metabolism. In reality, myocardial proteins of rodents, for example, are synthesised more during the daylight period when they rest and sleep (Rau and Meyer, 1975), and the same is true of epiphyseal cartilage (Simmons, 1968).

We shall consider why the balance between degradation and synthesis in tissues should vary so much with activity and rest, why it is that sleep with large EEG slow waves is 'worth more', and why, too, scratching by itchy patients at night tells us something about sleep's restorative properties. Only when those restorative properties can be measured shall we be able to assess the complaint of insomniac patients that sleep leaves them still exhausted. Actually the rectal temperature of poor sleepers does not fall as low (Monroe, 1967), which may mean relatively higher rates of degradation and, thus, less restorative sleep.

Several indirect indicators link sleep with synthetic processes. Growing infants sleep a lot. Wolff and Money (1973) found that a group of children of short stature had grown only one-third as fast at times of poor sleep as of good. Analyses across many animal species have shown a strong correlation between sleep duration and metabolic rate (Zepelin and Rechtschaffen, 1974). The higher the metabolism by day, the higher the relative degradation, and longer sleep could mean greater compensatory synthesis. In men, the customary individual duration of sleep correlates positively with the individual's waking body temperature, and thus, probably, with waking metabolic rate (Taub and Berger, 1976). Daily metabolism correlates highly with log body weight (Kleiber, 1961) and so does the amount of REM (paradoxical) sleep that individual men and women get (Adam, 1977).

## SLEEP AND ITS HORMONES

There are two types of sleep that alternate, one named NREM, or orthodox sleep, and the other REM, or paradoxical sleep. Human NREM sleep is divided into four stages, according to the EEG. Stages 3 and 4 are called slow-wave sleep, or SWS.

The return of interest to sleep's restorative role came with the Japanese discovery of a link between SWS and the large nocturnal secretion of human growth hormone (GH) (Takahashi *et al.*, 1968; Honda *et al.*, 1969). The secretion depends upon the presence of SWS (Sassin *et al.*, 1969; Schnure *et al.*, 1971) and this itself indicates that sleep is a time that facilitates anabolic processes in man. Growth hormone stimulates amino acid uptake into tissues, promotes protein and RNA synthesis (Korner, 1965), and has wide interreactions, such as stimulating red blood cell formation indirectly through erythropoietin (Peschle *et al.*, 1972). It raises blood free fatty acids, whose subsequent degradation is a source of cellular energy (ATP), thereby saving amino acids from catabolism and increasing their availability for protein synthesis during sleep.

Corticosteroids stimulate protein catabolism (Ardeleanu and Sterescu, 1973; Friedman and Strang, 1966) and the nocturnal peak of GH secretion comes at that time in the 24 hours when corticosteroids are lowest. Consequently, there is even greater net protein synthesis during human sleep, as demonstrated by Rudman *et al.* (1973) who injected GH and found significantly greater nitrogen retention after a 2300-hours dose than after a dose at 0800 hours.

Three other sleep-dependent human hormones are known; prolactin (Sassin *et al.*, 1973), luteinising hormone and testosterone (Boyar *et al.*, 1974; Rubin *et al.*, 1976): all four promote anabolism.

## SLOW-WAVE SLEEP FOR COMPENSATORY RESTORATION

Sleep seems to compensate for the degree of waking activity. After sleep-deprivation, men have extra SWS (Berger and Oswald, 1962; Williams *et al.*, 1964), and monkeys extra GH (Jacoby *et al.*, 1975). The longer the wakefulness prior to a nap, the more the SWS and GH (Karacan *et al.*, 1974). Even one hour of extra wakefulness during the night is followed by extra SWS and GH in the later night (Beck *et al.*, 1975). Extra exercise leads cats to have more SWS (Hobson, 1968), ordinary men get more HGH (Adamson *et al.*, 1974), and athletes greater amounts of SWS (Baekeland and Lasky, 1966; Shapiro *et al.*, 1975; Maloletnev and Telia, 1975; Zloty *et al.*, 1973).

Thyroid hormone increases degradation, and whereas hypothyroid patients lack SWS (Kales *et al.*, 1967), hyperthyroid patients have an excess of it and more GH (Dunleavy *et al.*, 1974). After days when normal men have had higher thyroxine secretion they get more SWS (Johns *et al.*, 1975). Acute starvation increases both SWS (MacFadyen *et al.*, 1973) and GH (Parker *et al.*, 1972; Karacan *et al.*, 1973) at a time when the latter's protein-sparing action would be of importance, while after chronic starvation an increase of SWS is associated with



**Table 1.** Mitoses maximal during the time of rest and sleep. (It is important to remember that this is during the light period in rodents.)

Species	Tissue	Reference
<b>Ectodermal Tissues</b>		
Man	Epidermis	Fisher (1968)
Rat	Epidermis	Halberg <i>et al.</i> (1965), Chekulaeva (1969)
Rat	Corneal epithelium	Sigelman <i>et al.</i> (1954)
Mouse	Corneal epithelium	Vasama and Vasama (1958)
Frog	Crystalline lens epithelium	Kuznetsov <i>et al.</i> (1972)
Rat	Pineal parenchyma	Renzoni and Quay (1964)
Rat	Anterior pituitary	Nouët and Kujas (1975)
Hamster	Cheek pouch epithelium	Brown and Berry (1968), Izquierdo and Gibbs (1972)
Rat	Lachrymal, parotid and submandibular glands	Vonnahme (1974)
Pregnant mice	Mammary alveolar epithelium	Echave Llanos and Piezzi (1963)
Rat	Lip epithelium	Bertalanffy (1960)
Rat	Buccal mucosa	Bertalanffy (1960)
Rat	Anal epithelium	Bertalanffy (1960)
<b>Mesodermal Tissues</b>		
Man	Bone marrow	Mauer (1965)
Rat	Epiphyseal cartilage	Simmons (1964)
Rat	Bone marrow	Clark and Korst (1969), Hunt and Perris (1974), Uryadnitskaya (1974)
Mouse	Bone marrow	Clark and Korst (1969)
Rat	Kidney tubules	Sharipov (1967), Saetren (1972)
Rat	Thymus	Hunt and Perris (1974), Kirk (1972)
Rat	Inner enamel epithelium, incisor teeth	Gasser <i>et al.</i> (1972)
<b>Endodermal Tissues</b>		
Rat	Liver parenchyma	Vonnahme (1974), Jaffe (1954)
Mouse	Liver	Barnum <i>et al.</i> (1958)
Mouse	Squamous epithelium of tongue and oesophagus	Burns <i>et al.</i> (1976)
Rat	Rectal mucosa after injury	Reeve (1975)
Rat	Gastric epithelium	Clark and Baker (1962)
Rat	Lung interalveolar septa	Romanova (1966)
Rat	Duodenum	Scheving <i>et al.</i> (1972)
Mouse	Duodenum	Scheving <i>et al.</i> (1972)
Mouse	Colon	Chang (1971)

tissue-rebuilding (Lacey *et al.*, 1975). As will be mentioned later, SWS will also be most strongly associated with anabolic repair because metabolic rate is then at its lowest.

The hormones of higher organisms are sophisticated additions to more primitive controls. Table 1 lists tissues in which there is a higher mitotic rate during the rest and sleep period of higher animals, but there could be added examples from the rest phases of lower organisms, in which the kind of hormonal mechanisms we have outlined could not be responsible. At the simplest level, the unicellular organism has rhythms of activity, with food-gathering, on the one hand, and, on the other, of assimilation with repair or reproduction. Rhythms abound in living systems and, indeed, spontaneous oscillations about a mean are inevitable in any system subject to feed-back control.

### RHYTHMS AND THE ENERGY CHARGE

To sustain life an organism has to maintain a chemical composition that differs from its surroundings, and to do so it must expend energy. It must repair its structural molecules and it must reproduce, both activities involving biosynthetic, energy-using processes. The energy is furnished by the catabolism of food and fuel stores to yield ATP (adenosine triphosphate) and is released by cleavage of the terminal phosphate(s), leaving ADP or AMP (the adenosine di- and monophosphates). These energy-releasing reactions are enzymically coupled to synthetic reactions to supply the energy that drives them. The adenine nucleotides AMP, ADP and ATP accept, store and transfer chemical potential energy and constitute a link among all the cell's activities. These include the maintenance of chemical gradients (e.g.  $\text{Na}^+/\text{K}^+$  pumps), active transport, and energy for motor activity. Hence, the adenine pool is a link between activity/inactivity rhythms and the catabolic/anabolic balance of the cell.

To achieve co-ordination, some universal, internal signal must operate to enhance or inhibit the cell's chemical activities, all of which can be broadly divided into energy-yielding (ATP-producing) reactions and energy-using (ATP-depleting) processes. It is the energy state of the cell that provides that signal. Its influence on metabolic pathways has been defined by Atkinson (1968), who proposed that the level of energy charge,

$$\text{EC} = \frac{\text{ATP} + \text{ADP}/2}{\text{ATP} + \text{ADP} + \text{AMP}},$$

varying within a range up to unity, determines the relative rates of flux through ATP-producing and ATP-depleting pathways. Lower values of EC favour ATP-producing pathways and higher values of EC promote ATP-utilising sequences.

The loci of control are regulatory enzymes that are sensitive to the levels of the adenine nucleotides and catalyse the irreversible steps in biochemical sequences.

Irreversible steps mean that the end-product of a synthetic sequence is not degraded by the reverse of the synthetic pathway and, hence, the rates of synthesis and degradation can be controlled by a single signal that modifies the activities of the regulatory enzymes in both synthetic and degradative pathways simultaneously. The EC level provides such a signal and affects these pathways in opposite ways. Degradative pathways yield ATP and so raise the EC of a cell. A higher level of EC then acts as a signal to reduce the rate of degradation. Synthetic pathways depend on ATP to drive them and are promoted by higher levels of EC. If EC falls, it is a signal to increase degradation and curtail synthesis as the system tries to restore a higher EC, which is thermodynamically more stable (Goldbeter, 1974).

The control enzymes have response curves with steeper slopes in the region of higher EC, and physiological values lie in the highly responsive, 'cross-over' portion of the graphs (Chapman *et al.*, 1971; Atkinson, 1970) where small changes in EC can disproportionately alter the relative rates of synthesis and degradation (Fig. 1). In addition, both types of EC response curves can be modified by the concentration of the biosynthetic end-product in such a way that if, for example, a synthetic end-product were in short supply, then the responsiveness to EC of the control enzymes in the synthetic pathway would be increased and synthesis enhanced (Fig. 2).

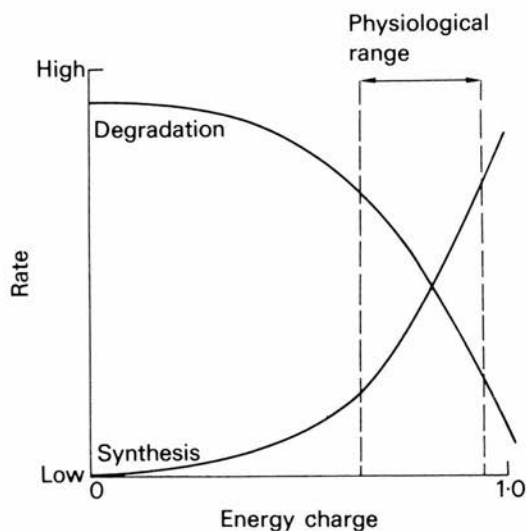


Fig. 1. In the physiological range small changes in energy charge have a big effect.



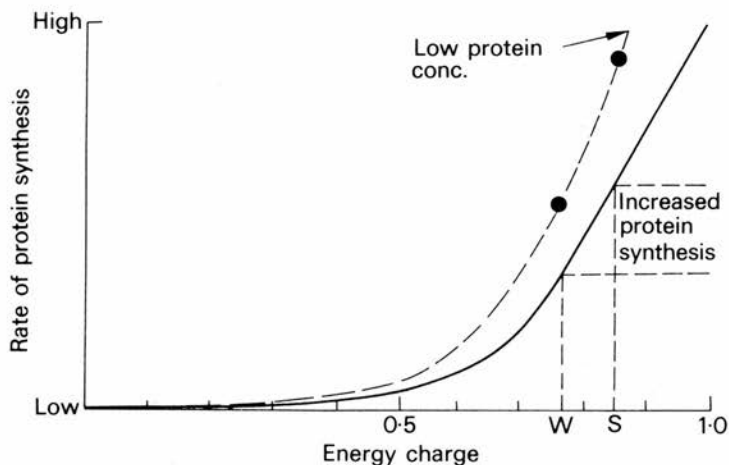


Fig. 2. The difference in energy charge between wakefulness and sleep may be small but it has a big effect — even bigger if end-product concentration is low.

#### *Protein Synthesis, Growth and Activity*

The concept of energy charge was originally applied to intermediary metabolism but the steps in protein synthesis, too, are sensitive to change in adenine nucleotides (Walton and Gill, 1975; Ayuso-Parrilla and Parrilla, 1975) and changes in EC are synchronised with growing and non-growing phases of *Escherichia coli* (Chapman *et al.*, 1971).

The simple organism's oscillations between rest and activity must induce concomitant fluctuations in EC and so, in turn, in other cellular processes. Motor activity demands ATP, so motility and food-gathering will lower EC, promote degradative processes, and temporarily suppress biosynthesis. During subsequent rest, the EC will rise and conditions become optimal for the biosynthetic processes previously curtailed, and these would be the greater with an added signal of low protein concentration.

Evidence that motility does inhibit synthetic processes can be seen in an experiment where the unicellular *Stentor coeruleus* was cut in half, such that each half received an equal share of the macronucleus, but only one half had the ciliary apparatus. Subsequent onset of mitotic activity took place much earlier in the cilia-free end (Guttes and Guttes, 1959); the EC must have risen during the enforced rest of the non-ciliated end and acted as a trigger for synthetic processes.

#### SYNTHESIS DURING REST IN HIGHER ORGANISMS

In complex organisms, motility and responsiveness to the environment are not characteristics of each cell, but the same principles apply. The house cricket,

*Acheta domesticus*, has a 24-hour rhythm of RNA and protein synthesis in its brain and sub-oesophageal ganglion, with synthesis highest when these insects are inactive. Their activity increases sharply with the onset of darkness, whereupon synthesis of RNA and protein in the brain falls to its lowest (Cymborowski and Dutkowski, 1969, 1970).

Higher organisms store fuel foods to allow prolonged activity without feeding. During such activity the energy-requiring biosynthetic pathways will be suppressed by a downward shift in the EC, which will stimulate catabolic processes in muscle. Additional tissues will be influenced by concurrent hormone release or, if their substrates for ATP production and synthesis of macromolecules are diverted, as fuel for motor activity.

In human muscle two minutes of exercise lowers ATP by 25 per cent (Karlson and Saltin, 1970) and in rat muscle EC and ATP likewise fall (Crabtree and Newsholme, 1972; Newsholme and Start, 1973; Wojciechowska *et al.*, 1975). Conversely, protein synthesis in rat diaphragm muscle (Robolledo and Gagliardino, 1971) and myocardium (Rau and Meyer, 1975) are higher during the resting/sleeping period. As examples of tissues linked indirectly, protein synthesis falls in the hypothalamus if rats exercise (Bordeianu and Butculescu, 1971) and protein synthesis in rat skin is at its highest during the daylight, when rats rest and sleep (Chekulaeva, 1969). In man, exercise inhibits skin mitosis for many hours afterwards (Fisher, 1968). Peaks in mitotic rate in frog crystalline lens epithelium coincide with episodes of motor inactivity, whereas troughs are associated with active periods (Kuznetsov *et al.*, 1972). It is important to distinguish such phenomena from the increased use of tissues that leads to their subsequent hypertrophy. The latter involves the activation of genetic material in the nucleus, with increased formation of RNA, and, subsequently, of proteins (Meerson, 1975).

Mitosis depends upon synthesis, whether for tissue maintenance or propagation of the species. There is a strong relationship between mitotic activity and higher concentrations of ATP (Guttes and Guttes, 1959). A fall in ATP below a critical level inhibits mitosis (Epel, 1963). A positive correlation between the rhythm of ATP level and cell division has been shown for *Tetrahymena pyriformis* (Plesner, 1964) and, as Table 1 showed, most tissues have a maximum mitotic rate during the resting/sleeping period, when ATP and EC levels must be highest. It seems that, through evolution, rhythms of mitosis have become entrained to the variations of energy state associated with the rest-activity cycle.

### *Human Sleep is More Than Rest*

Rest reduces ATP depletion and so metabolic rate falls. Sleep is more than rest, it is a state of unresponsiveness brought about by active nervous mechanisms, a form of rest that ensures that the whole body, including the nervous system, can recuperate.

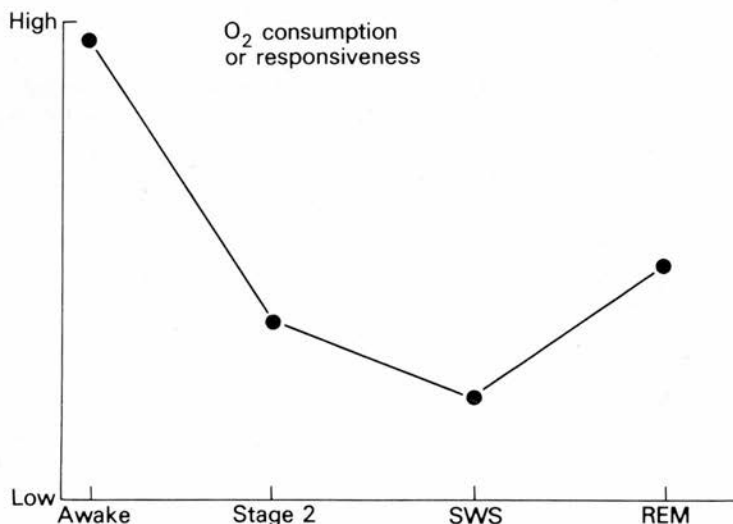


Fig. 3. In stages 3 + 4 (slow wave) sleep, responsiveness is lowest to auditory signals, scratching is least, blood pressure is lowest, and whole-body oxidative metabolism is lowest: the demands of cellular work, that compete with the needs of synthesis, are at their lowest.

The stages of human sleep differ in their degrees of unresponsiveness, with stage 2 being a less responsive state than wakefulness or drowsiness, and SWS a state of even lesser responsiveness, while REM sleep is about equal to stage 2.

These relationships in the degree of responsiveness are true for response to auditory stimuli (Williams *et al.*, 1966), blood pressure reflexes (Coccagna *et al.*, 1971), or scratching by patients with itchy skins (Savin *et al.*, 1975). Precisely the same relationships are true also of the metabolic rates that accompany these undisturbed sleep stages (Fig. 3). Human metabolic rate is some 10 per cent lower in stage 2 than in wakeful rest, with a further 2 per cent fall during SWS (Brebbia and Altshuler, 1968). Why it is that SWS is 'worth more' (Dement and Greenberg, 1966) can be understood in terms of the low metabolic rate (low cellular work) at that time, when lower oxygen consumption means less degradation, in response to higher EC, which, in turn, promotes a higher rate of protein synthesis. A 2 per cent margin does not seem large but one must remember that the events concerned are on the steep, highly responsive part of the curve in Fig. 2, where a small shift in EC leads to a disproportionate change in the rates of both synthesis and degradation.

## SLEEP AND THE BRAIN

It is the brain that controls sleep and it is brain functions such as the power to sustain attention that are most obviously impaired by sleep deprivation. Although



the mature brain no longer grows, it still needs synthetic activity. It rivals the liver in its high rate of turnover of proteins and nucleic acids, consistent with its role in information processing, storage and retrieval, which rely on synthetic activity over and above the protein synthesis required for enzymes and renewal of structural components. The benefit of sleep is most obvious for the brain because during mere rest the nervous system remains responsive to the environment, whereas in sleep it becomes unresponsive (Steriade, 1970). The responsiveness of the wakeful cortex depends upon sustained ascending activation from the mesencephalic reticular formation, and the high levels of extracellular  $K^+$  so caused (Katzman and Grossman, 1975). These higher levels of  $K^+$  are closely coupled to higher energy consumption by the ATPase ion pump (Bachelard, 1975a; Jobsis *et al.*, 1975; Lowry, 1975).

Brain protein synthesis has its highest rates at the time when rats rest and sleep (Gordon and Scheving, 1968; Richardson and Rose, 1971; Rose *et al.*, 1969). The cat has several sleep periods and with each of these there is a rise in the protein content of perfusates from the brain (Drucker-Colin *et al.*, 1975). Jones (1971) found that brain ATP levels of golden hamsters were higher during sleep. The protein and RNA content of supraoptic nuclei was higher in sleeping rats than waking rats, while the latter, in turn, had a higher content than sleep-deprived animals (Doemin and Rubinskaya, 1974). Van den Noort and Brine (1970) measured the ATP, ADP and AMP concentrations in rat brain after 13 hours of sleep deprivation and after one hour of subsequent sleep. Calculations of EC using their results give a value of 0.77 after 13 hours of sleep deprivation but 0.83 after the one hour of subsequent sleep. This rise is in the highly responsive portion of the curve, and Fig. 2 illustrates how protein synthesis in the brain would differ under these two conditions and how there could be additional enhancement of protein synthesis during sleep at a time when end-product concentration would presumably be low, enabling us to understand why men who have suffered prolonged sleep deprivation can be restored by fewer hours of sleep than those they lost.

### *NREM-REM Cycles*

The different physiology of NREM and REM sleep suggests that they differ in function, but a causal interrelationship has been proposed because NREM always precedes REM sleep (Hartmann, 1973). During SWS the majority of neurones have a much reduced firing rate compared with waking (McGinty *et al.*, 1974) and since activation from the reticular formation is at its lowest, ATP depletion would be reduced and the EC level would rise, whereas during subsequent REM sleep the higher firing rate (McGinty *et al.*, 1974) would be expected to lower intracellular ATP and stimulate brain glycolysis and respiration.

The amount of REM sleep has been thought to correlate with the required intensity of brain synthetic activity (Oswald, 1969, 1970, 1976; Stern and

Morgane, 1974). However, it is in REM sleep that skeletal muscles are at their most relaxed, and their ATP, EC and net protein synthesis must be maximal. If higher rates of brain protein synthesis were to occur during REM sleep itself in conjunction with the higher rate of cell-firing, this would imply compartments of ATP pools between, for example, neurones and glia, or intracellular compartments within neurones, as for glucose transport (Bachelard, 1975b).

In higher organisms, protein is synthesised at the rate of two amino acids per second, which means 1 to 2 minutes to synthesise a medium-sized protein molecule (Dintzis, 1961), in addition to the time required to initiate the process. Oscillations have been found in the rate of protein synthesis in a remarkable diversity of tissues (Brodsky, 1975). There is a theoretical minimum oscillation period of the order of minutes, because of the inertia in the protein synthetic machinery (Goodwin, 1963). The REM periods of most species last only a few minutes, and this is so short a time that the onset of a REM period could not be the primary initiator of any increased brain protein synthesis associated with that period, though peak rates of brain protein synthesis could coincide with the onset of REM periods. It is tempting to speculate with Brodsky (1975) that these oscillations in the rate of protein synthesis underlie NREM-REM sleep cycles.

## CONCLUSIONS

It has been apparent for some years that sleep is a time that favours synthetic processes but previous communications (Oswald, 1969, 1976) had no biochemical base; the survey now presented has been refined by the first author, K.A.

It appears that the rest/activity cycle of simple organisms and the sleeping/waking rhythm of higher animals induce concomitant fluctuations in cellular work and, hence, in the cellular energy charge. As a consequence, metabolic balance alters so that degradative processes are stimulated during activity or waking, and restorative, synthetic processes are inevitably favoured during inactivity and sleep.

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## MOTHER'S RUIN

The College sometimes takes pride in its eighteenth century opposition to the sale of gin. But two physicians started the whole business. In 1635 the royal physicians, Sir Theodore de Mayerne and Dr Cadyman, obtained from His Majesty a patent for 'the sole exercise of a new way of distilling strong waters and making vinegar out of cider, perry and buck whereof they are the inventors'. Two years later they joined up with other distillers of spirits, whisky, and geneva or gin to be granted a charter of incorporation as the Distillers Company. The gin trade was slow off the mark. In the year 1690 a total of 43,000 gallons was distilled, paying a duty of tuppence a gallon. By 1721 the output had risen to 2,800,000 gallons and many were worried that the common people were sodden with gin 'like opium with the Turks'. The College felt gin drinking had become a hazard to health and in 1725 petitioned the House of Commons for legislation to curb gin production having 'observed with concern for some years the fatal effects of several sorts of distilled spirits upon great numbers of both sexes rendering them diseased, not fit for business, poor - and too often the cause of weak feeble and distempered children, who must be instead of an advantage and strength, a charge to the country'. Perhaps as a result of this the government doubled the duty on gin and by 1741 the yearly output had risen to 7,500,000 gallons. It was Henry Fielding's prose and Hogarth's pictures that finally brought a halt to this alcoholic epidemic.

## Further studies of scratching during sleep

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### SUMMARY

Fifteen patients with a variety of itching skin diseases (atopic eczema, dermatitis herpetiformis, lichen planus, urticaria and psoriasis) have been studied in the sleep laboratory. Recordings were made of all-night electroencephalogram, electro-oculogram, submental electromyogram, and muscle potentials from both forearms.

Bouts of scratching during orthodox (NREM) sleep occurred more frequently in stages 1 and 2 than in stages 3 and 4. The frequency in paradoxical (REM) sleep was close to that in stage 2 sleep. This pattern was similar for all the diseases studied and seems to be related to the physiology of the sleep stages rather than to the skin diseases themselves. The mean duration of the bouts of scratching was not related to the sleep stage in which they started.

We have previously reported (Savin, Paterson & Oswald, 1973) that patients with atopic eczema scratch during all stages of sleep, and that the incidence of scratch bouts varies in the different stages. We now report our findings on a larger group of patients with a variety of skin diseases.

### *Patients*

Three groups of patients have been studied:

*Group I.* Five patients with atopic eczema: four for 1 night and one for 2 nights. Four of these patients formed the basis of our previous report.

*Group II.* Five patients with dermatitis herpetiformis: four for 2 nights and one for 1 night. The diagnosis in all cases had been confirmed by skin biopsy and response to dapsone.

*Group III.* A miscellaneous group of five patients for 1 night each. Three patients had lichen planus, one had urticaria, and one an itchy psoriasis.

### METHODS

Patients were studied in the sleep laboratory as before (Savin, Paterson & Oswald, 1973). They slept



in conditions of low illumination at a constant room temperature ( $18^{\circ}\text{C}$ ) and remote from all recordings. The early patients in the series were observed on closed-circuit television allowing all movements, including scratching, to be noted by hand on the moving paper record. Our experience, gained in this way, allowed us to dispense with television after it became clear that bouts of scratching could be identified by their rhythmical quality using the recordings on the paper trace from the forearm leads. Most of the body movements during the night were associated with scratching.

Recordings were made of all-night electroencephalogram (EEG), electro-oculogram, submental electromyogram and muscle potentials from both forearms. Records were analysed in 20 s periods in terms of wakefulness and the usual stages of sleep: that is orthodox (non-rapid eye movement or NREM) sleep, with its stages, 1, 2, 3 and 4, and paradoxical (rapid eye movement or REM) sleep (Rechtschaffen & Kales, 1968).

The records were examined for:

- (a) The duration of each bout of scratching.
- (b) The stage of sleep in which the bout started.

Our method did not allow us to gain information about the amplitude of the scratching movements nor the frequency of the individual scratch strokes.

In addition we determined:

- (c) The time spent in each sleep stage during the night.
- (d) The number of bouts of scratching starting during each stage of sleep.
- (e) The frequency with which bouts of scratching started during each stage.
- (f) The duration of the bouts of scratching while asleep and while awake.

Several tests were used in the statistical examination of the data:

- (1) Analysis of variance, a technique that allows a simultaneous comparison of more than 2 variables, was used to compare the duration of scratch bouts in the different stages of sleep.
- (2) Correlated *t*-tests for paired observations in order to compare the duration of scratch bouts for each subject when in different sleep stages.
- (3) Kendall's rank correlation test was used to investigate possible correlations between the durations, or between durations and frequencies, of scratching bouts in different stages of sleep. This test only takes into account the ordering and not the absolute values of the results.

## RESULTS

### *Frequency of bouts starting in each stage of sleep*

The results for the three groups of patients are shown in Fig. 1.

Scratching was most frequent in stage 1 and this was true of all three groups. The frequency decreased through stages 2, 3 and 4. As we found before, REM sleep was in an intermediate position (Table 1). The difference between stages 1 and 2 was significant ( $t=4.06$ , d.f. = 14,  $P<0.01$ ). There was also a significant difference between stage 2 and stages 3 and 4 combined ( $t=2.64$ , d.f. = 14,  $P<0.02$ ). There was no significant difference between stage 2 and REM sleep, between stages 3 and 4 and REM sleep, or between wakefulness and stage 1.

### *Duration of bouts of scratching starting in each stage*

The details of the three groups of patients are shown in Table 2.

There was no significant difference in the length of bouts starting in the different stages of sleep, when one-way analysis of variance was undertaken (d.f. = 3.42;  $f=0.112$ ; n.s.). Although intersubject

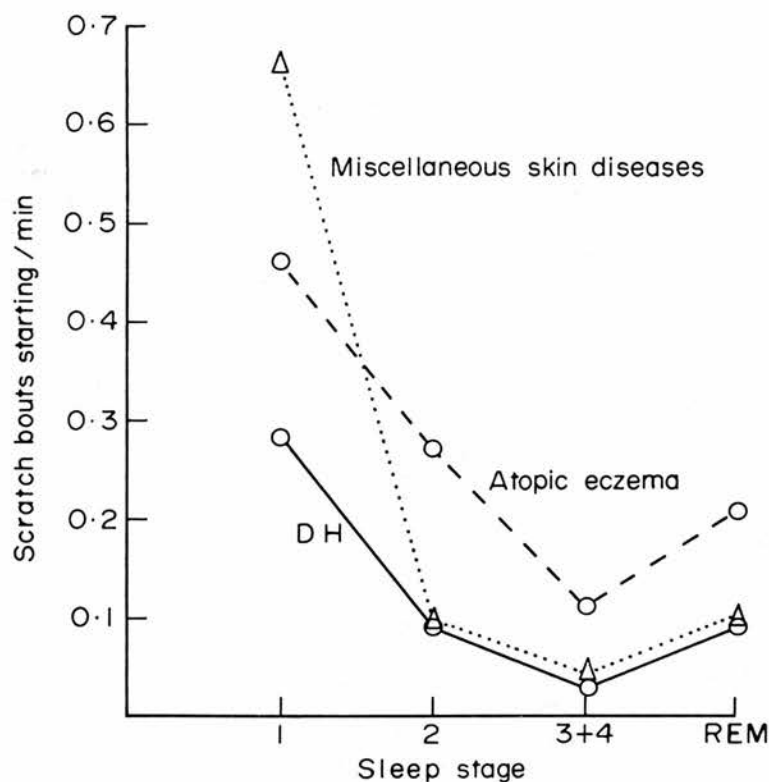


FIGURE 1. The frequency of bouts of scratching starting in each stage of sleep.

TABLE 1. Mean frequency and standard deviation of scratching bouts starting in wakefulness and each stage of sleep in scratches/min

Patients	Sleep stage				
	Awake	1	2	3+4	REM
Atopic eczema (n=5)	0.47 ± 0.04	0.46 ± 0.40	0.27 ± 0.26	0.11 ± 0.07	0.21 ± 0.22
Dermatitis herpetiformis (n=5)	0.47 ± 0.08 (n=3)	0.28 ± 0.11	0.09 ± 0.02	0.03 ± 0.01	0.09 ± 0.06
Miscellaneous group (n=5)	0.37 ± 0.29	0.66 ± 0.37	0.09 ± 0.12	0.04 ± 0.05	0.10 ± 0.10
Overall means (n=15)	0.43 ± 0.18 (n=13)	0.47 ± 0.34	0.15 ± 0.18	0.06 ± 0.06	0.13 ± 0.15

TABLE 2. Mean duration of bouts of scratching starting in wakefulness and in each stage of sleep. Mean  $\pm$  s.d. (s/bout)

Patients	Sleep stage					Average 1,2,(3+4) & REM
	Awake	1	2	3+4	REM	
Atopic						
eczema (n=5)	17.7 $\pm$ 5.6	10.4 $\pm$ 3.4	11.5 $\pm$ 5.2	12.7 $\pm$ 6.0	10.8 $\pm$ 5.0	11.4 $\pm$ 4.5
Dermatitis						
herpetiformis (n=5)	11.5 $\pm$ 4.2	8.5 $\pm$ 2.9	10.3 $\pm$ 4.1	9.6 $\pm$ 4.7	7.0 $\pm$ 0.6	8.9 $\pm$ 2.6
Miscellaneous						
group (n=5)	13.8 $\pm$ 5.5	12.5 $\pm$ 2.0	11.7 $\pm$ 4.4	10.0 $\pm$ 2.4	14.1 $\pm$ 7.8	12.1 $\pm$ 3.0
Overall means (n=15)	14.3 $\pm$ 5.4	10.5 $\pm$ 3.1	11.2 $\pm$ 4.3	10.8 $\pm$ 4.5	10.6 $\pm$ 5.8	10.8 $\pm$ 3.5

variation was high (d.f. = 42.14;  $f = 4.52$ ,  $P < 0.01$ ), the means for each stage were strikingly similar—approximately 10 s duration per bout.

The significant intersubject variation was analysed further, revealing a characteristic duration of scratching for each person, that is to say a patient who tended to have particularly long bouts of

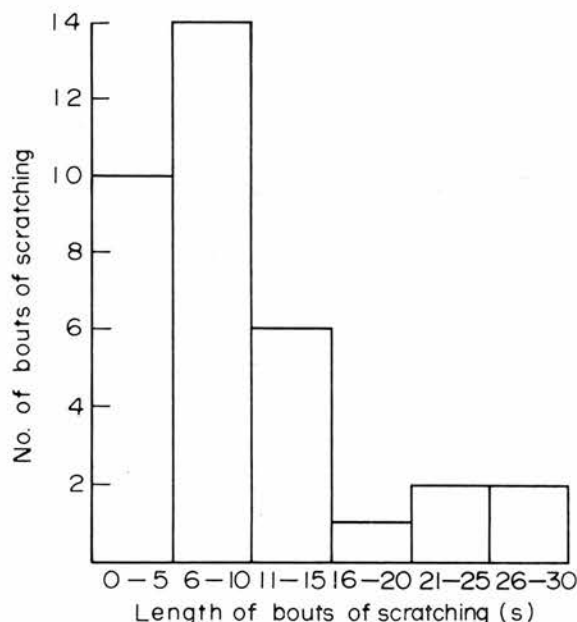


FIGURE 2. The duration (s) of all scratch bouts recorded during stage 1 sleep on a single night of one patient with dermatitis herpetiformis.



TABLE 3. Correlations ( $\tau$ ) and their significance level between different stages of sleep

Durations of scratch bouts in	Stage 1	Stage 2	Stages 3+4	Stage REM
Stage 1		$\tau = 2.69$ $P > 0.01$		
Stage 2			$\tau = 2.55$ $P > 0.05$	$\tau = 2.29$ $P > 0.05$
Stages 3+4				$\tau = 2.29$ $P > 0.05$

scratching during stage 1 sleep would, on average, sustain this lengthy pattern through the other stages of sleep. Kendall's ranking test revealed a correlation between the individual subject's mean duration of bouts in one stage when compared with the other stages of sleep (Table 3).

Individual scratch bouts vary considerably in duration even in the same person in a single stage of sleep (Fig. 2).

#### *Scratching while awake*

Bouts of scratching were also recorded when the patients were in bed but awake. There was no significant difference between the frequency of occurrence of scratch bouts during wakefulness and during stage 1 of sleep. However, bouts of scratching when the patients were awake lasted significantly longer on average ( $14.3 \pm 5.4$ s), than during sleep ( $10.8 \pm 3.5$ s);  $t = 3.77$ , d.f. = 14,  $P < 0.01$ .

#### DISCUSSION

In our previous paper we showed that in atopic eczema bouts of scratching occurred more frequently during sleep stages 1 and 2 than in 3 and 4, with paradoxical sleep in an intermediate position. We have now found this pattern also in patients with other itchy skin diseases such as dermatitis herpetiformis, lichen planus and urticaria (Fig. 1); in other words, this may be a general phenomenon and not one simply confined to atopic eczema.

The nature of the chemical agents causing the itching in these conditions is not well understood; but, in such dissimilar diseases, the agents involved may well not be the same. It seems unlikely that the chemicals involved would vary in the same way in all these diseases during the different stages of sleep. The differences between the frequency with which bouts of scratching occur in these stages can be linked more plausibly to changes in the excitability of the central nervous system than to alterations in the skin lesions themselves. The frequency with which bouts occur during the different stages is consistent with the order of general reactivity of these stages as judged by other criteria; for example, the threshold of response to auditory stimuli (Williams, Morlock & Morlock, 1966), and the level of blood pressure (Coccagna *et al.*, 1971).

In experimental animals there is a spinal reflex pathway for scratching, but in man scratching may be a 'reaction rather than a reflex, demanding the integrity of at least some part of the brain for its performance.' (Sinclair, 1973). We have shown that, while the frequency of bouts of scratching varies among the stages of sleep, the duration of the bouts themselves does not. Bouts of scratching last, on average, just as long whichever stage of sleep they start in. At first sight, this suggests an 'all or none' type of response, in which the size of the reaction is fixed and independent of the stimulus, provided

this is over a threshold value. However, Sherrington (1966) demonstrated that this is not the case in experimental animals, in whom the greater the stimulus, the longer and more vigorous is the bout of scratching which follows. Reviewing our figures in this light, it is clear that there is considerable variation in the length of scratch bouts even for one person in a single sleep stage (Fig. 2). It is only the means which are the same. If scratching during sleep is a reflex action, our findings suggest that the excitability of the arc is greatly influenced by the stage of sleep, while the motor side, as judged by the length of the scratch bouts, is not. During wakefulness, bouts of scratching were frequent (Table 1), and lasted significantly longer than during any of the stages of sleep; perhaps a conscious 'deliberate' component had been added.

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